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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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GASTROENTEROLOGY-UROLOGY DEVICES PANEL

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June 27, 2013
8:00 a.m.

Holiday Inn
2 Montgomery Village Avenue
Gaithersburg, Maryland

PANEL MEMBERS:

MARK A. TALAMINI, M.D.	Acting Panel Chair
ABDELMONEM A. AFIFI, Ph.D.	Non-Voting Member
CHRISTIAN P. PAVLOVICH, M.D.	Non-Voting Member
KAREN L. WOODS, M.D.	Non-Voting Member
LAWRENCE Y. AGODOA, M.D.	Temporary Non-Voting Member
DOUGLAS M. COLDWELL, Ph.D., M.D.	Temporary Non-Voting Member
SRINIVASAN DASARATHY, M.D.	Temporary Non-Voting Member
ASHLEY L. FAULX, M.D.	Temporary Non-Voting Member
JON C. GOULD, M.D.	Temporary Non-Voting Member
ERIC S. MARKS, M.D.	Temporary Non-Voting Member
MARVA M. MOXEY-MIMS, M.D.	Temporary Non-Voting Member
GERALD SCHULMAN, M.D.	Temporary Non-Voting Member
STEVEN D. SCHWAITZBERG, M.D.	Temporary Non-Voting Member
DANIEL W. SIMON, M.D.	Temporary Non-Voting Member
MARIA H. SJOGREN, M.D., M.P.H.	Temporary Non-Voting Member
DAVID R. RUTLEDGE, Pharm.D.	Industry Representative
CYNTHIA CHAUHAN, M.S.W.	Patient Representative
MILDRED D. FENNAL, M.S.N., Ph.D.	Consumer Representative
SHANIKA CRAIG, M.H.A., M.B.A.	Designated Federal Officer

Free State Reporting, Inc.
1378 Cape St. Claire Road
Annapolis, MD 21409
(410) 974-0947

FDA REPRESENTATIVES:

BENJAMIN FISHER, Ph.D.
Director, Division of Reproductive, Gastro-Renal, and Urological Devices
Office of Device Evaluation

MARJORIE SHULMAN, M.B.A.
Director, Premarket Notification (510(k)) Program
Office of Device Evaluation

JONETTE FOY, Ph.D.
Deputy Director for Engineering & Science Review
Office of Device Evaluation

CAROLYN NEULAND, Ph.D.
Chief, Renal Devices Branch
Division of Reproductive, Gastro-Renal, and Urological Devices
Office of Device Evaluation

HERBERT LERNER, M.D.
Deputy Director, Division of Reproductive, Gastro-Renal, and Urological Devices
Office of Device Evaluation

JEFFREY W. COOPER, D.V.M.
Division of Reproductive, Gastro-Renal, and Urological Devices
Office of Device Evaluation

MORGAN LISCINSKY
Press Contact

FDA PRESENTERS:

GEMA GONZALEZ, M.S.
Division of Reproductive, Gastro-Renal, and Urological Devices
Office of Device Evaluation

DOUGLAS M. SILVERSTEIN, M.D.
Division of Reproductive, Gastro-Renal, and Urological Devices
Office of Device Evaluation

OZLEM TOPALOGLU, Ph.D., M.P.H.
Division of Epidemiology
Office of Surveillance and Biometrics

BRANDEN REID, Ph.D.
Division of Reproductive, Gastro-Renal, and Urological Devices
Office of Device Evaluation

GANG CHEN, M.D., Ph.D.
Division of Epidemiology
Office of Surveillance and Biometrics

CARRIE RAINIS, Ph.D.
Division of Postmarket Surveillance
Office of Surveillance and Biometrics

FRANK P. HURST, M.D.
Division of Reproductive, Gastro-Renal, and Urological Devices
Office of Device Evaluation

OPEN PUBLIC HEARING SPEAKERS:

JENNIFER YTTRI, Ph.D.
Senior Fellow
National Research Center for Women & Families

LEROY LESLIE HAMILTON, Ph.D.
Concerned Citizen

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M E E T I N G

(8:10 a.m.)

DR. TALAMINI: Good morning, everybody. It's approximately 8:10, and I would like to call this meeting of the Gastroenterology-Urology Devices Panel of the Medical Devices Advisory Committee to order.

I am Dr. Mark Talamini, the Chairperson of this Panel. I am a gastrointestinal surgeon. I'm Chief of GI Surgery at the University of California, San Diego.

I note for the record that the voting members present constitute a quorum as required by 21 C.F.R. Part 14. I would also like to add that the Panel participating in the meeting today has received training in FDA device law and regulations.

For today's agenda, during Session I, the Panel will discuss and make recommendations regarding the proposed classification of sorbent hemoperfusion systems, one of the remaining pre-amendments Class III devices. The Class III sorbent hemoperfusion system is a device intended for the treatment of poisoning, drug overdose, hepatic coma, and metabolic disturbances. The Panel will also discuss whether the proposed special controls are adequate to reasonably ensure the safety and effectiveness of sorbent hemoperfusion devices labeled for the treatment of poisoning and drug overdose.

During Session II, the Panel will discuss and make

recommendations regarding the proposed classification of implanted blood access devices for hemodialysis from Class III to Class II. The Class III implanted blood access devices for hemodialysis include various flexible or rigid tubes such as catheters and cannulae. The Panel's discussion will involve making recommendations regarding regulatory classification to either reaffirm Class III or reclassify these devices into Class II and comment on whether special controls are adequate to reasonably ensure the safety and effectiveness of this device.

Before we begin, I would like to ask our distinguished Panel members and FDA staff seated at this table to introduce themselves. Please state your name, your area of expertise, your position, and affiliation. And if we could begin with Dr. Fennal at the far left, please.

DR. FENNAL: Good morning. My name is Dr. Mildred Fennal. I am the Director of the International Nursing Education Consortium, as well as the president of a national nursing organization. My expertise is in critical care nursing.

DR. RUTLEDGE: I'm David Rutledge, with Abbott Vascular. I'm a director in their global clinical research, and my expertise is in clinical trial design as a clinical trialist for over 25 years. I'm the Industry Representative.

MS. CHAUHAN: Cynthia Chauhan, Patient Representative.

DR. SCHWAITZBERG: Steve Schwaitzberg, Chief of Surgery at Cambridge Health Alliance at the Harvard Medical School. My expertise is

device development and minimally invasive surgery. I'm a former IRB chair.

DR. PAVLOVICH: Christian Pavlovich. I'm a urologist at Johns Hopkins, and my specialty is urologic oncology, and this is my second or third year involved in such panels.

DR. COLDWELL: I'm Doug Coldwell. I'm an interventional radiologist at the University of Louisville. I'm chief of interventional there. My area of expertise is unresectable liver tumors and their treatment, as well as device placement.

DR. MOXEY-MIMS: Marva Moxey-Mims. I'm a pediatric nephrologist. I'm at the NIH, at NIDDK, and I oversee the clinical research program for the kidney, urology, and hematology division.

DR. GOULD: Jon Gould. I'm Chief of General Surgery at the Medical College of Wisconsin, and I am a gastrointestinal surgeon.

DR. WOODS: Karen Woods. I'm a gastroenterologist in private practice, now in Houston, Texas. I'm a Clinical Associate Professor of Medicine at Baylor, where I was full-time faculty for 12 years, doing primarily endoscopy and endoscopic research, and now I'm your average clinician doing regular clinical practice. I've been on this Panel, I think, 15 years in various capacities in one way or another, so I enjoy being here again. Thank you.

MS. CRAIG: Shanika Craig. I'm the Designated Federal Officer for this meeting.

DR. TALAMINI: Mark Talamini, Acting Panel Chair, as advertised.

DR. SIMON: I'm Dr. Dan Simon. I'm an interventional radiologist. I'm Medical Director of the Vascular Access Center of West Orange, and I've been doing this for two years on these panels.

DR. FAULX: I'm Ashley Faulx. I'm Associate Professor of Medicine at Case Medical Center, and I'm the Director of Endoscopy at the Cleveland VA Medical Center, and my area of expertise is therapeutic endoscopy and endoscopic research.

DR. SJOGREN: I'm Maria Sjogren. I am a gastroenterologist and in numerous specialties, and I work at Walter Reed National Military Medical Center and at Georgetown University.

DR. AGODOA: I'm Larry Agodoa. I'm at the NIH/NIDDK, Office of the Director. I'm the Director of the End-Stage Renal Disease Program.

DR. DASARATHY: I am Dasarathy. I'm from the Cleveland Clinic. I'm a transplant hepatologist.

DR. SCHULMAN: I'm Gerald Schulman. I'm a Professor of Medicine at Vanderbilt University and director of the clinical trials of nephrology at Vanderbilt.

DR. AFIFI: I'm Abdelmonem Afifi. I'm Professor and Dean Emeritus of the Fielding School of Public Health at UCLA, and I'm a biostatistician.

DR. FISHER: I'm Ben Fisher, the Division Director of the Division of Reproductive, Gastro-Renal, and Urological Devices. I would like to thank the Panel for their participation this morning.

DR. TALAMINI: Thank you, Panel members.

If you have not already done so, please sign the attendance sheets that are on the table by the doors.

Ms. Craig, the Designated Federal Officer for the Gastroenterology-Urology Devices Panel, will make some introductory remarks.

Ms. Craig.

MS. CRAIG: Good morning. The FDA Conflict of Interest Disclosure Statement, Gastroenterology-Urology Devices Panel of the Medical Devices Advisory Committee, June 27th, 2013.

The Food and Drug Administration is convening today's meeting of the Gastroenterology-Urology Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act (FACA) of 1972. With the exception of the industry representative, all members and consultants of the Panel are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with Federal ethics and conflict of interest laws covered by, but

not limited to, those found at U.S.C. 18 Section 208 of the Federal Food, Drug and Cosmetic Act are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this Panel are in compliance with the Federal ethics and conflict of interest laws. Under U.S. Code 18 Section 208, Congress has authorized FDA to grant waivers to special Government employees and regular Federal employees who have potential financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussions of today's meeting, members and consultants of this Panel have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of U.S. Code 18 Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

Today's agenda is broken into two sessions. Both are particular matters of general applicability.

Session I. The Panel will discuss and make recommendations regarding the proposed classification of sorbent hemoperfusion systems, one of the remaining pre-amendments Class III devices. I'm sorry, Class II devices.

The Class III sorbent hemoperfusion system is a device intended for the treatment of poisoning, drug overdose, hepatic coma, and metabolic disturbances. The Panel will also discuss whether the proposed special controls are adequate to reasonably assure the safety and effectiveness of sorbent hemoperfusion devices labeled for the treatment of poisoning and drug overdose.

Session II. The Panel will discuss and make recommendations regarding the proposed classification of implanted blood access devices for hemodialysis from Class III to Class II. The Class III implanted blood devices for hemodialysis include various flexible or rigid tubes such as catheters and cannulae. The Panel's discussion will involve making recommendations regarding regulatory classification to either reaffirm Class III or reclassify these devices into Class II and comment on whether special controls are adequate to reasonably assure the safety and effectiveness of this device.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, no conflict of interest waivers have been issued in accordance with U.S. Code 18 Section 208.

Dr. David Rutledge is serving as the Industry Representative, acting on behalf of all related industry, and is employed by Abbott Laboratories.

We would like to remind the members and consultants that if

the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record. FDA encourages all other participants to advise the Panel of any financial relationships that they may have with any firms at issue.

For the duration of the Gastroenterology-Urology Devices Panel on June 27th, 2013, the following individuals have been appointed as temporary non-voting members.

Dr. Maria Sjogren and Dr. Srinivasan Dasarathy are special Government employees and consultants to the Gastrointestinal Advisory Committee in the Center for Drug Evaluation and Research.

Ms. Cynthia Chauhan is a consultant to the Oncologic Drugs Advisory Committee at CDER.

These individuals have undergone the customary conflict of interest review and have reviewed the materials to be considered at this meeting.

The appointment was authorized by Jill Hartzler Warner, J.D., Acting Associate Commissioner for Special Medical Programs, on June 24th, 2013.

A copy of this statement will be available for review at the registration table during the meeting and will be included as a part of the

official transcript.

Before I turn the meeting back over to Dr. Talamini, I would like to make a few general announcements.

Transcripts of today's meeting will be available from Free State Court Reporting, Incorporated, telephone number (410) 974-0947. Information on purchasing videos of today's meeting can be found at the FDA meeting registration table.

The press contact for today's meeting is Morgan Liscinsky.

I would like to remind everyone that members of the public and the press are not permitted in the Panel area, which is the area beyond the speaker's podium. I request that reporters please wait to speak to FDA officials until after the Panel meeting has concluded.

If you are presenting in the Open Public Hearing today and have not previously provided an electronic copy of your slide presentation to FDA, please arrange to do so with Ms. AnnMarie Williams at the registration desk.

In order to help the transcriber identify who is speaking, please be sure to identify yourself each and every time that you speak.

Finally, please silence your cell phones and all other electronic devices at this time. Thank you.

Dr. Talamini.

DR. TALAMINI: We will now hear from Marjorie Shulman,

M.B.A., Director, Premarket Notification (510(k)) Program.

I would like to remind the public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the Panel Chair.

Ms. Shulman.

MS. SHULMAN: Good morning. My name is Marjorie Shulman. I'm Director of the Premarket Notification Program, and I'm going to give you some background on device reclassification and why we're here today.

The purpose of this Panel meeting is to provide input to FDA on the classification of pre-amendment device types and whether FDA should call for PMAs or reclassify these into Class II or Class I.

A pre-amendment device is a device type that was introduced into interstate commerce prior to May 28th, 1976, the enactment date of the Medical Device Amendments.

Recent legislation (FDASIA) that was passed last summer has affected the classification of medical devices, including the Class III 510(k)s. And now FDA must publish a proposed order announcing our proposed classification and seek public comment, hold a panel meeting if classifying or reclassifying a device type, and consider comments and all available information, including panel recommendations, prior to issuing a final order finalizing the classification of the device.

So what are the device classes? A device should be placed in

the lowest class whose level of control provides reasonable assurance of safety and effectiveness, and classified devices are based on the controls necessary: Class I general controls, Class II general and special controls, and Class III premarket approval.

General controls include prohibition against adulterated or misbranded devices, good manufacturing practices, registration of the manufacturing facility, listing of the devices they make there, and recordkeeping, etc.

Special controls include performance standards, postmarket surveillance, patient registries, and development and dissemination of guidelines, et cetera.

Class I is for devices which general controls are sufficient to provide reasonable assurance of the safety and effectiveness. Class I devices typically do not require a premarket review prior to being marketed.

And continuing on for Class I devices: devices that cannot be classified into Class III because they are not life-sustaining, life-supporting, of substantial importance in preventing impairment of public health, and because they do not present an unreasonable risk of illness or injury; also devices that cannot be classified into Class II because insufficient information exists to establish special controls to provide reasonable assurance of the safety and effectiveness.

Some examples of Class I devices: general manual

gastroenterology and urology surgical instruments, enema kits, protective garments for incontinence.

What are Class II devices? Devices that cannot be classified into Class I because the general controls are insufficient to provide reasonable assurance of safety and effectiveness and there is sufficient information to establish special controls to provide such assurance. Class II devices typically require premarket notification (510(k)) prior to being marketed.

Some examples of Class II devices: hemodialysis, lithotripters, stents, dialysis systems, and gastrointestinal feeding tubes.

So how are special controls used? As an example, percutaneous transluminal coronary angioplasty (PTCA) catheters were reclassified from Class III to Class II and to special controls. FDA issued a special controls guidance to mitigate the risk to health, which included biocompatibility testing, performance testing, animal testing, clinical information, sterilization and shelf life, and labeling, which addressed warnings, precautions, adverse effects, etc. These special controls, in combination with the general controls, provide reasonable assurance of the safety and effectiveness. Companies must provide evidence in their 510(k) submission of how the special controls were addressed.

Class III is for devices that cannot be classified into Class II because insufficient information exists to determine that general and special

controls are sufficient to provide reasonable assurance of the safety and effectiveness, and these devices are life-sustaining and/or life-supporting, or of substantial importance in preventing impairment of human health, or present a potential unreasonable risk of illness or injury. Class III devices typically require premarket approval, otherwise known as PMA, prior to being marketed.

Some examples of Class III devices: implanted urinary and fecal incontinence devices, injectable bulking agents for gastro-urology use, intragastric implants for morbid obesity, and extracorporeal photopheresis systems.

What are Class III 510(k) devices? Those are pre-amendment devices where FDA issued a proposed rule classifying them as Class III, however, no final rule was issued, or a final rule was issued for Class III but the rule did not contain a date by which companies were required to submit a PMA. Therefore, these Class III devices are allowed to proceed via the 510(k) process until such time either a call for PMAs or a reclassification is finalized.

The reclassification process: The FDA may reclassify a pre-amendment device in a proceeding that parallels the initial classification proceeding, based upon new information respecting the device, either on FDA's own initiative or upon the petition of an interested person. The Agency classifies or reclassifies intended uses which have been reviewed by the Agency.

Here is a chart that explains the previous slides on how we look at classification. If general controls are sufficient, it can go into Class I. Also, if it's life-supporting or life-sustaining and important to human health and there's a potential unreasonable risk of illness or injury and the answer is no, and then sufficient information for special controls, no, it can go into Class I. If it's life-supporting or life-sustaining and substantially important to human health and the answer is yes, but there is sufficient information to establish special controls, it can go into Class II; the answer to those are no, then it would be Class III.

So what do we need from the Panel today? We would like your input on classification of these devices which are the subject of the Panel session. The input should include an identification of the risk to health, if any, presented by the device; whether the device is life-sustaining, life-supporting, or of substantial importance in preventing impairment to human health, or presents an unreasonable risk of illness or injury; whether sufficient information exists to develop special controls and the identification of such special controls.

After the Panel meeting, the FDA will issue a proposed order proposing classification of the device and seeking public comment on the proposal. FDA has proposed that, based on the device type, either it will be reclassified or split the classification based on indications. FDA will consider the available evidence, including the input of this Panel and the public

comments. FDA will issue a final order identifying the appropriate class.

If Class II, devices may continue to be marketed. If Class III, existing devices will remain on the market but must submit a PMA by a specified time frame to continue marketing. If a PMA is not approved, devices will be considered misbranded and must be removed from distribution.

Thank you.

DR. TALAMINI: I would like to thank Ms. Shulman for her presentation.

Does anyone on the Panel have clarifying questions for Ms. Shulman?

(No response.)

DR. TALAMINI: Hearing none, we will now hear from the FDA.

I would go off script just for a moment to tell the Panel members, it's very important to listen carefully to this presentation because we will be answering questions based upon it immediately afterwards. So focused attention on the part of the Panel is much appreciated for this presentation.

So we'll now hear from the FDA.

MS. GONZALEZ: Thank you. Good morning. My name is Gema Gonzalez. I'm a reviewer with the Renal Devices Branch. Welcome.

Today we're here to talk about the reclassification and

regulation of sorbent hemoperfusion systems. As you heard, these are one of the remaining pre-amendment Class III devices that were classified as Class III but for which PMAs were never called, and therefore, they have been reviewed under the 510(k) program. Of course, Class III devices are primarily brought to market through the approval of a premarket approval application, or PMA, not a 510(k). And so, to resolve this discrepancy, we are undertaking this reclassification effort, and with your help, we hope to come to a determination as to whether they should remain in Class III and call for PMAs or be down-classified to Class II for some or any other uses.

Therefore, the objectives of today's meeting are to discuss the risks to health posed by sorbent hemoperfusion systems in their various clinical uses; discuss whether there is sufficient evidence of safety and effectiveness to establish special controls for these devices for their various uses; to discuss FDA's proposals for special controls for sorbent hemoperfusion systems used for poisoning or drug overdose; and to discuss FDA's proposals for the classification of these devices for their various indications for use.

To accomplish these goals, you'll hear from a series of FDA presentations. I'll start with an introduction and some regulatory background, and then you'll hear from Dr. Doug Silverstein, who will provide the clinical background and his clinical review. Dr. Ozlem Topaloglu will provide her review of the literature search that she performed. And

Dr. Silverstein will come back and provide a final summary and FDA's recommendations.

So what are these devices, the sorbent hemoperfusion systems, that we're discussing today? They are identified and presented here, the regulatory definition as it appears in the Code of Federal Regulations, C.F.R. Part 876.5870. And, accordingly, these are devices that consist of an extracorporeal blood system similar to that identified in the hemodialysis system and accessories regulation, which is Part 876.5820, and a container filled with absorbent material that removes a wide range of substances, both toxic and normal, from blood flowing through it. The absorbent materials are usually activated carbon or resins which may be coated or immobilized to prevent fine particles entering the patient's blood. The generic type of device may include lines and filters specially designed to connect the device to the extracorporeal blood system, and the device is used in the treatment of poisoning, drug overdose, hepatic coma, or metabolic disturbances. And as you can see, for all of those uses, it's currently classified as Class III.

I should mention that hemodialysis systems and accessories are mentioned here in the regulation. You can see them under Part 876.5820. However, they are separate devices, independent devices, they have their own regulation, and they're not under discussion today for reclassification. They do have some similarities in technological characteristics, but that's the mention there.

In use, these devices, as mentioned, form extracorporeal systems containing a filter or a cartridge with the absorbent material. The blood circulates, of course, through the extracorporeal circuit and passes through the cartridge or a filter to remove the toxins. These are typically activated charcoal technologies. It may consist of a standalone filter or a cartridge or a whole comprehensive system, including pumps and filters and the extracorporeal tubing all as part of the same device. The absorber removes a wide range of substances, both toxic and normal, from the circulating blood. You'll hear more about these specific devices in the coming presentations.

The indications for use: As mentioned, there are four that are specifically listed in the regulation: poisoning, drug overdose, hepatic coma, and metabolic disturbances. We'll hear about all four today. In many cases, we do talk about the poisoning and drug overdose uses together because of their similarities.

This chart summarizes the 510(k)s that have been cleared under this regulation. The time span actually is from 1983, so it's a period of about 30 years. And as you can see, there have been ten 510(k)s that have been cleared from six devices and five different manufacturers. It's important to show that about half of the devices cleared were standalone filters and the other half have been comprehensive systems, pumps and filters and the whole system. Also, about half of them have the drug

overdose use labeling, and the other half include combined labeling of drug overdose and hepatic coma.

It's important to mention that only two 510(k)s have been cleared since 1999. Those were from the Gambro Renal Products, the MARS device, Molecular Absorbent Recirculating System, which gained clearance for drug overdose and later for hepatic encephalopathy.

Therefore, there are just ten 510(k)s, just a limited experience, as you can see, since these have been regulated.

Through these 510(k)s, the indications for use have been revised slightly. As you saw, the four main indications for use listed in the regulation are hepatic coma, metabolic disturbances, drug overdose, and poisoning. However, through the 510(k)s, the labeling has been expanded somewhat, and today we'll see hepatic encephalopathy due to decompensation of chronic liver disease, acute or chronic hepatic coma, or hepatic failure.

To provide some background on the regulation of these devices, as you heard, these are pre-amendment devices, meaning that they were commercialized and available prior to the enactment of the Medical Device Amendments in 1976. At that time, classification panels were convened to discuss these devices, all the devices that were currently available, discussed the risks to health and based on those risks classified them, as you heard, into Class I, II, or III.

The classification panel that discussed these devices actually met in July of 1978. They came up with a list of the risks to health, which you'll see in the next slide, and based on those risks they decided that the devices fit the classification for Class III -- they're life-sustaining and life-supporting devices -- and the panel felt that there was not sufficient evidence to write and establish special controls that may provide sufficient reasonable assurance of safety and effectiveness. Therefore, the recommendation was to place these devices in Class III, and FDA followed suit. We published our proposed rule in 1981, proposing a Class III classification. That rule was finalized in 1983, again specifying that these devices would be under Class III. Unfortunately, during that final rule, a date for the submittal of PMAs was not specified. So, throughout the classification process, initially, the devices were placed in Class III, but the date for a PMA was never specified and the devices continued under 510(k).

This is the list of the risks to health that were identified in 1978 by that original classification panel. As you can see, it includes risks associated with the extracorporeal circuit, things such as platelet loss or blood loss, release of emboli, clotting, infection; but it also includes risks associated with the use of the filter, such as depletion of vital nutrients, hormones, or vitamins; infection and metabolic disturbances.

To continue, in April of 2009, FDA published a 515(i) order under the 515(i) provision of the Act, requiring information on these devices

so that a reclassification process could start. Again, we were trying to resolve that discrepancy of the review. One response was received to this 515(i) order, and this was received in support of down-classification of the devices when labeled for drug overdose or poisoning. That reclassification petition did not mention the hepatic coma and metabolic disturbances uses.

FDA reviewed the reclassification petition as well as the clinical evidence and all the information and regulatory history and regulatory experience with these devices, and we issued our recommendations for reclassification in February of 2012 in a proposed rule that was published in the *Federal Register*. There was a comment period associated with that. However, later on that year, as you heard, the FDA Safety and Innovation Act was enacted and came into effect immediately, and that changed the reclassification process. According to the Act, it now needs to have a proposed order rather than a proposed rule and also convene a classification panel.

The proposed order was published in April of 2013. Again, the same reclassification scheme that we were proposing in 2012, we repeated those, and the same reasons, and there was also a public comment period until May of 2013. And, of course, the reclassification panel is where we are today.

Here are the recommendations that FDA is making. As published in the 2012 proposed order as well as the proposed rule of 2013,

we're recommending a split classification for this regulation. We recommend that for these devices for use in drug overdose or poisoning, that they be down-classified to Class II. We feel that although they are life-supporting and life-sustaining, they do meet the definition of Class II because there is sufficient evidence that we can establish special controls to provide a reasonable assurance of safety and effectiveness.

However, for the hepatic coma and metabolic disturbances uses, we feel there is not sufficient information to establish special controls and that these devices should remain Class III and we should call for a PMA.

I'd like to now turn our attention to the clinical evidence that we have been considering to come to our recommendations. We'll first look at medical device reports that have been received to FDA. I'll give you an introduction to that, and then the following talks will concentrate on the literature review and the clinical experience and evidence that we have.

We have done a search of our medical device reports. As you know, when adverse events occur in clinical practice, they can be submitted to FDA as a medical device report, and we have a database, the Manufacturer and User facility Device Experience, or MAUDE database, that receives and stores that information.

We can do searches and get a snapshot of the postmarket experience that we have with these devices and get information on how they're being used and what is happening in use. When we were doing our

searches, we were looking at the reports received between January 1st of 1998 and March 24th of 2013, just to get a snapshot of a 15-year period. We were looking for things such as device breaks, leaks, dislodgment, vascular injury, or problems in placement. However, in our searches we did not find any MDRs, any medical device reports, with these devices.

We think that the lack of reporting here might be because of problems with underreporting of all adverse events, not just in these types of devices, but spread overall in the industry. Also, when reports are submitted, sometimes there's incomplete information and we're not able to make assessments. There might be problems with the manufacturer reporting practices. This is a passive system, a voluntary system for reporting adverse events, and so there are some limitations. And, of course, as you saw, we believe there's lack of clinical use in the cleared uses in the few devices that have been cleared through the years.

I'd now like to introduce Dr. Doug Silverstein, our medical officer, who will provide a clinical background on these devices.

Thank you.

DR. TALAMINI: If I could just ask. It's a little tough to hear at this end of the room, for whatever reason, so if you could speak directly into the microphone, that would be very helpful. Thank you.

DR. SILVERSTEIN: Good morning. My name is Doug Silverstein, and I'm a nephrologist, a pediatric nephrologist, and a medical officer in the

Renal Devices Branch.

To reiterate what Gema Gonzalez has already stated, the indications for use for sorbent hemoperfusion systems, they are used in the treatment of poisoning, drug overdose, hepatic coma, and metabolic disturbances.

This is a general schema of what the circuit may look like. It typically looks like a hemodialysis circuit where you have blood that flows from the patient. There's an arterial pressure sensor and a blood pump, which then pumps the blood in by about 200 mL to 250 mL per minute. It eventually goes through an absorption column, which is similar to, but not identical to, what you might see with a typical hemodialysis dialyzer. It is then returned back to the patient via a venous pressure sensor and an air detector and then returned back to the patient. So, the circuit looks very similar to what you would see in a hemodialysis circuit, but there are differences which we will describe.

Hemoperfusion was first introduced in the 1940s, but its active use was not observed really in the United States until about the 1970s. Each treatment takes about two to three hours, although some patients may require one treatment and some patients may require multiple treatments.

As Gema Gonzalez has already stated, the blood is pumped through a column that has sorbents. Those act as the attractants for the materials that may accumulate in various diseases that require

hemoperfusion. The absorbent materials are usually activated carbons or resins. They may be coated or immobilized to prevent fine particles from entering the patient's blood. And the substances which are attracted to the absorbent materials include those in molecular weight from 100 Da to 40,000 Da. So, a very wide range of substances can be trapped by these systems.

These sorbents include synthetic resins which remove lipid- and protein-soluble substances; ion exchange resins, which remove ionic and organic substances; activated carbon; and as Gema Gonzalez has already reported to you, in the charcoal hemoperfusion systems, they are coated with charcoal, which irreversibly binds drug and chemicals and is able to remove water- and protein-soluble substances. So, various systems have been developed depending on what the need is.

Hemoperfusion provides a variety of benefits. First of all and foremost, it provides a clearance of toxic substances which may accumulate in a variety of conditions. It can be used for the treatment of pericarditis, patients with gastrointestinal systems and diseases, as we talked about with hepatic coma; lethargy; patients with cardiac dysfunction and patients with peripheral nerve disorders such as nerve conduction velocity disorders.

These systems enable the clearance of organic acids, indoles, myoinositol, amino acids, and other hormones and metabolites. The tremendous advantage of these is that there is very low protein loss. And I'll describe a system in which this is enabled.

And, finally, some of the systems combine hemoperfusion with hemodialysis. That's hemodiabsorption. That permits solute clearance, such as small solutes like creatinine and urea, and some larger molecules, which are called middle molecules, which may accumulate in various conditions.

For drug overdose and poisoning, hemoperfusion is very useful. Compared to hemodialysis, hemoperfusion is often superior for the removal of certain poisons and drugs, depending on the type of substances. Lipid- and protein-soluble substances of various molecular weights are effectively removed, whereas larger substances are mostly retained, another advantage to the system so you don't remove substances that are undesired to be removed.

The efficacy of hemoperfusion for drug overdose and poisoning is very dependent on the treatment early after the exposure. If a reasonable amount of time passes between the exposure and the attempt to provide the therapy, it may not be as efficacious because those have already entered into the tissues.

This chart just shows you a simple version of what might be removed by hemoperfusion compared to hemodialysis. Hemoperfusion more effectively removes the substances here on the left part of the slide, such as phenobarbital, barbiturates, theophylline, digitalis, and acetaminophen, whereas those that are more effectively removed by hemodialysis include salicylates, ethylene glycol, methanol, and lithium.

So, depending upon the exposure, if it's known, you might choose hemoperfusion compared to hemodialysis.

For hepatic failure and coma, there is a different story. Hepatic coma is the final state of hepatic encephalopathy, in which brain function progressively deteriorates. These systems are used to compensate for liver failure by removing toxins from the blood, although as we'll mention this later on, we don't always know what those substances are. Data shows that hepatic coma-related hospitalizations are associated with prolonged and costly hospital stays, and in-hospital mortality for hepatic coma is nearly 8%. So, the desire to have a system or some therapy to treat patients with hepatic coma is significant.

There are a couple of systems I want to highlight. The first is the BioLogic-DT system used for hepatic coma. It is also called, generically, "liver dialysis." It combines hemodialysis with hemoperfusion. The blood flow rate is a little bit lower than you might see for patients, like adults, who may be receiving hemodialysis, about 200 mL to 250 mL per minute. These contain sorbent-based, or charcoal, parallel or flat-plate dialyzers.

The dialyzer contains charcoal, but it also may contain other substances, including a cation which can bind ammonia, which may accumulate in hepatic disease. It also contains sodium chloride, bicarbonate, and glucose, and amino acids, depending upon what you want to return back to the patient or what you want to bind.

The loading of the substances on the charcoal permits their return back to the patient. So if a patient is acidotic, you might want to have the bicarbonate, which can then be transmitted back to the patient. Some patients with hepatic disease have hypoglycemia, so you want glucose in there to return back to the patient. There is high drug clearance with low protein binding.

This is a typical picture of what the BioLogic-DT looks like. In patients who have liver disease, hepatic coma, you see a high amount of toxin, and the patients have a low amount of glucose (hypoglycemia). What happens is that there is a prime in the system which delivers glucose into the charcoal portion of the system. This is the membrane, itself. The glucose then traps -- in the suspension here, it traps the toxin and glucose is returned back to the patient and the toxin is removed. So, the charcoal itself binds the toxin and also traps the glucose. So, in effect, at the end, there is a lower amount of toxin and a higher amount of glucose in the patient.

Another system is the called the Molecular Absorbent Recirculating System, or MARS, or extracorporeal albumin dialysis. And this really, if you look at it simply, is like a typical hemodialysis system, but in addition, it has an albumin circuit. Blood is removed from the patient. Here is your blood circuit and here is your dialysate circuit and the albumin circuit is part of the system, and it is done to regenerate albumin so that you have an ability to bind protein substances.

Blood is circulated, albumin is constantly regenerated, and then it passes through the filter over here. Basically what you have are parallel circuits, and the purpose of this is to combine hemodialysis with the hemoperfusion to trap the protein-bound substances which may accumulate in various conditions.

For metabolic disturbances, we really didn't find a very good amount of information regarding these. These defined disorders are characterized by the loss of metabolic balance, including patients with liver and kidney failure. Examples include newborns with inborn errors of metabolism, like PKU patients, with diabetes or thyroid disease. These patients may exhibit a variety of different symptoms, including respiratory difficulty, altered mental status, seizures, and organ failure.

We were able to find two studies in which they discussed the use of hemoperfusion for metabolic disturbances. There was a basic science study in 1984 that showed that hemoperfusion significantly reduces various amino acids in rats. And, there was a clinical study in 1981 of nine patients, and it showed that hemoperfusion effectively removes various substances, including phenols and uric acid, in the majority of patients. They found that these disorders, the treatment of which is they receive hemoperfusion, resulted in very few adverse effects.

I would now like to pass the discussion to Dr. Ozlem Topaloglu, who will discuss the systematic literature review of sorbent hemoperfusion

systems.

DR. TOPALOGLU: Good morning. My name is Ozlem Topaloglu. and I'm an epidemiologist in the Office of Surveillance and Biometrics, Division of Epidemiology. I will be presenting the findings from the systematic literature review on the safety and effectiveness of sorbent hemoperfusion systems.

DR. TALAMINI: Excuse me. I'm sorry, this is Talamini, the Panel Chair. A little closer to the microphone for us. Thank you very much.

DR. TOPALOGLU: Sure. I will first provide a brief description of the objective of the review and the methodologies applied. Then I will present the results supported in the literature on the safety and effectiveness of sorbent hemoperfusion systems, followed by strengths and limitations of this literature review and a summary.

The objective of this literature review is to summarize the safety and effectiveness of the use of sorbent hemoperfusion systems in the treatment of poisoning, drug overdose, hepatic failure in a coma, and metabolic disturbance.

A search of PubMed and the Cochrane Library was conducted on May 3rd, 2013, using the search terms shown here. All articles were limited to human studies published in English, RCTs, observational studies with more than 50 patients, and systematic reviews and meta-analyses, with no limitation for the publication date.

The initial search resulted in 598 unique articles. The titles and abstracts were reviewed to identify clinical studies, case reports, systematic reviews, and meta-analyses. Of the 598 articles, 324 were excluded; 274 full-text articles were further reviewed to exclude observational studies with sample size less than 50 and case reports and series. Five articles were added by cross-referencing. At the end, 27 articles were included in this literature review.

Please note: Since the Panel Executive Summary was sent out, three additional articles were included due to the delay in the availability of the full-text articles.

Of the 27 articles included, 15 were RCTs, 8 were observational studies, and 4 were systematic reviews and meta-analyses. Per indication, 3 studies were on poisoning, 4 were on drug overdose, and 20 were on hepatic failure. There were no articles identified on metabolic disturbance with the criteria of this literature review.

Now I will discuss the safety and effectiveness of the sorbent hemoperfusion systems by indication. I will first present the studies on poisoning and drug overdose.

For these indications, we identified seven studies, of which one was a small RCT and six were observational studies. A total of 609 patients from the United Kingdom, United States, Taiwan, China, and Czechoslovakia were included. In these studies, in general, patients were treated for

acetaminophen, theophylline, and phenobarbital overdose and paraquat and dichlorvos poisoning.

The studies reported different outcomes; therefore, I will highlight some of the study results.

For poisoning, the first study reported that, with the use of four different types of charcoal hemoperfusion, almost 100% removal of paraquat at 15 minutes was achieved. In a second study, 67 patients received hemoperfusion, while 41 patients received standard medical therapy. A significantly lower mortality rate was observed in the hemoperfusion group compared to SMT.

For drug overdose, the first study shown in the table was a small RCT that randomized patients to receive either charcoal hemoperfusion or SMT. In this study, there appeared to be no survival benefit achieved with the hemoperfusion.

In Koffler et al., 54 patients were treated for multiple drug overdose. Patients with phenobarbital intoxication improved the most, and almost all of these patients were discharged 3 to 25 days after admission.

Regarding safety, one study reported that no serious hypotensive or anaphylactic reactions to charcoal hemoperfusion were observed. Two studies reported that, in patients treated with hemoperfusion, platelet counts decreased below normal range. One study reported that there was no serious bleeding.

Now I will discuss the studies on hepatic failure and coma. I will present the study results in four subsections: first, studies on charcoal hemoperfusion, then BioLogic-DT and MARS, and lastly, systematic reviews and meta-analyses.

For charcoal hemoperfusion, there were two concurrently conducted RCTs and one large observational study. All three studies were from the United Kingdom. In the first trial, 10-hour daily hemoperfusion was compared to standard of medical therapy. In the second trial, five-hour daily hemoperfusion was compared to 10-hour daily hemoperfusion. The overall survival rates were similar in both groups in these two trials. These studies also suggested that survival is related with the etiology of the liver failure, such as patients with hepatitis and acetaminophen overdose benefit the most.

The third study was an observational study with 620 patients. The survival rate was presented as the trends in survival rate over the time period from 1973 to 1985. Here you see the trends in survival over time by etiology of the liver failure.

None of these studies provided any safety information on adverse events.

For BioLogic-DT, four small RCTs were identified whose sample size ranged from 10 to 20 patients. Regarding survival, three of the studies reported this information. Ellis et al. was the only study that chose survival as

the study endpoint, and they reported that there were no survivors in either of the study groups. Hughes et al. reported that one out of five patients treated with BioLogic-DT and three out of five in the control group survived. Wilkinson et al. reported that three out of six patients treated with BioLogic-DT and zero out of four patients in the control group survived. Kramer et al. did not provide survival data.

Regarding safety, two studies reported that there were no adverse events observed. One study reported that a major complication observed was disseminated intravascular coagulation. One study reported clotting in the circuit due to poor blood flow. There was inconsistent reporting on the decrease in platelet counts. Two studies reported that excessive platelet consumption was not observed, whereas two other studies reported that a large decrease in platelet count was observed.

For MARS, nine RCTs were identified. In these studies, a total of 249 patients were treated with MARS and 235 with standard of medical therapy. Seven RCTs compared MARS to SMT. Two RCTs compared MARS to other therapies such as plasma exchange and Prometheus absorption and recirculation system.

The cause and type of liver failure varied in these studies. Seven RCTs included patients with acute-on-chronic liver failure, and two RCTs included patients with chronic liver failure.

MARS treatment varied from 3 to 10 sessions, with variable

treatment duration per session. Duration of follow-up varied from 7 days to 180 days.

The studies which reported data on survival in hepatic encephalopathy are summarized in this slide. Among those five studies, significant short-term survival benefit was shown by the use of MARS in two studies highlighted in orange. However, long-term survival of six months, reported in Heemann et al., was similar in both groups as 50%. The other three studies highlighted in pink did not show a significant survival benefit with MARS. Finally, the study reported in Hassanein et al. was not designed to formally assess the difference in survival in these two groups.

Regarding improvement in hepatic encephalopathy, the definition in assessment for this outcome varied among the studies. Additionally, the time point for assessment varied and they were short term.

Regardless of the definitions, three out of five studies showed a statistically significant improvement in hepatic encephalopathy in patients treated with MARS compared to SMT, highlighted in orange. Similarly, two studies that did not show significant improvement in hepatic encephalopathy are highlighted in pink. Mitzner et al. did not provide data on hepatic encephalopathy.

Additionally, there was one observational study that was conducted in Germany. Sixty-seven patients were treated with MARS in addition to standard of medical therapy, and 82 patients received SMT alone.

Patients were followed for a mean of three years. The mean survival rates after three years were 33% in MARS-treated patients and 15% in the control group.

Regarding safety, Banares et al. reported that, at 90 days, there were no significant differences in the number of patients who had severe adverse events between the groups. Other reported adverse events included mild thrombocytopenia, fever and sepsis due to catheter, and hemodynamic instability.

Finally, there were four meta-analyses, of which two were on artificial and bioartificial support systems and two were on MARS. The first meta-analysis performed by the Cochrane Collaboration reported that, compared to SMT, artificial and bioartificial support systems had no significant effect on mortality, but had a significant beneficial effect on hepatic encephalopathy.

In subgroup analyses, artificial support systems appear to reduce mortality by 33% in acute-on-chronic liver failure, but not in acute liver failure. However, the second study reported survival benefit for patients with acute liver failure, but not with acute-on-chronic liver failure. These contradictory results appear to be due to the inclusion of two large RCTs published in 2004 and 2007 and were included in the second meta-analysis performed by Stutchfield.

There were two meta-analyses that specifically evaluated the

studies on MARS. These studies show that MARS treatment did not appear to result in reduced mortality. Additionally, Vaid et al. reported that MARS resulted in a significant decrease in total bilirubin levels and improvement in hepatic encephalopathy. In general, safety and adverse events were not collected systematically, or not at all, in the studies that comprised these meta-analyses.

Our literature review has some strengths and limitations. The strength of this literature review was the inclusion of RCTs and large observational studies, which are considered to be a higher level of evidence in the literature. There was also no limitation on the publication date in the search criteria, which allowed us to capture the range of literature over the years. However, observational studies with less than 50 patients and case reports and series were excluded, which can be considered a limitation. Additionally, we restricted our search in Medline database and PubMed and the Cochrane Library.

Now I would like to provide the summary of this literature review.

For drug overdose and poisoning, one small RCT and six relatively large observational studies were identified. Although the evidence is limited, these studies suggest that hemoperfusion may be a safe and effective method for treating multiple types of drug overdose and poisoning.

For hepatic failure and coma, there was one RCT with charcoal

hemoperfusion which did not show overall survival benefit but suggested that survival might be related with the etiology of the hepatic failure.

With BioLogic-DT, there were four RCTs which did not show a significant survival benefit. However, due to the very small sample size, it's difficult to draw conclusions.

With MARS, there were nine RCTs. In these studies mortality was not consistently shown to be improved. Some of the studies demonstrated improvement in liver function in hepatic failure -- hepatic encephalopathy. Safety data was not provided in all studies. Adverse events included thrombocytopenia and bleeding.

For metabolic disturbance, no studies were identified with the criteria for this literature review. Therefore, for this indication, we believe that there is insufficient evidence that sorbent hemoperfusion systems are safe and effective.

This concludes my presentation. Now Dr. Silverstein will continue with the summary and FDA recommendations.

Thank you.

DR. SILVERSTEIN: Good morning again.

Our summary for hemoperfusion for drug overdose and poisoning. We've been able to establish that there are often no alternative therapies to hemoperfusion for the removal of certain substances such as paraquat. And the studies, as Dr. Topaloglu has shown, show well-

understood risks for hemoperfusion for these indications.

The FDA believes that medical evidence strongly displays benefit over risk and that there is sufficient evidence to establish special controls for drug overdose and poisoning.

The Panel will therefore be asked whether the identified risks to health can be appropriately mitigated with the proposed special controls, and whether any additional or different special controls are recommended for the use of hemoperfusion for the treatment of drug overdose and poisoning.

The FDA assessment of risks with hemoperfusion were originally established by the original panel many years ago, and these included platelet loss and thrombocytopenia, blood loss, depletion of vital nutrients, the release of emboli, clotting, leukopenia, hemolysis, and the rest of these items on the chart.

Since that time we have been able to identify new risks pertaining to these devices. These include extracorporeal leaks, lack of effectiveness, lack of sterility, the depletion of certain drugs by the therapy, some problems with biocompatibility, the treatment interruptions or discontinuations, and problems with electric shock or electromagnetic interference.

The Panel will specifically be requested to comment on the risks to health and whether there are additional risks that should be

considered for these devices.

So, there are risks and there are mitigations, and for these, we believe there is establishment of special controls for drug overdose and poisoning. For example, the risks are noted on the left part of this slide and the mitigations on the right part of the slide. For example, platelet loss and thrombocytopenia, we believe, can be mitigated by special labeling. Blood loss can be mitigated by device design and mechanical integrity testing. Depletion of various nutrients and substances that can be lost by hemoperfusion can be mitigated by labeling and bench studies. The leak of absorbent emboli can be dealt with by device design and bench and elution testing. And clotting, leukopenia, and hemolysis all can be dealt with by mitigations via labeling or bench studies. And, finally, hypotension can be mitigated by special labeling.

The proposed special controls for drug overdose and poisoning include that the device must be demonstrated to be biocompatible. Performance data must be necessary to demonstrate the mechanical integrity of the device. Performance data should be available to demonstrate the device sterility and shelf life. Bench performance data should be available to demonstrate the device functionality and the extent of the substance removal according to the device labeling, and this should be validated by the device safeguards. And a summary of the clinical experience with the device should be available.

In addition, special labeling controls and recommendations must be consistent with the performance data and must include a list of drugs and/or poisonings that a device has been demonstrated to remove and the extent that the device removes these substances. Finally, for devices that incorporate electrical components, validation testing of electrical safety and electromagnetic compatibility must be available.

For hepatic coma and metabolic disturbances, as you've heard before, we were only able to identify two randomized controlled studies and one observational study. In the study from 1988, O'Grady et al. showed that the haemocol charcoal column did not improve survival in 137 patients with hepatic failure, regardless of the duration of hemoperfusion, 5 versus 10 hours. In another study in 1986, they showed that charcoal hemoperfusion did not improve outcomes in 620 patients with grade 3 to 4 hepatic encephalopathy, and safety data was not reported. That was the observational study.

For hemoperfusion for hepatic coma, we recognize that the BioLogic-DT does infer certain benefits, as shown on the left part of this slide. It combines hemodialysis with hemoperfusion, so you get removal of certain substances along with the clearance of certain solutes. Some studies have been able to show that there was improvement of hepatic function and reduced lactate levels, but this has not been consistently shown. Some studies show improved physiologic stability and enhanced glucose control.

And we do identify that there is proven biocompatibility.

However, as shown on the right part of this slide, there are significant risks. There are few reports of studies in humans, and therefore more studies, we believe, are required. These patients require catheters for any extracorporeal therapy, and therefore, there may be catheter complications. Some patients develop thrombocytopenia and decrease in fibrinogen. And, we found there was an inconsistent removal of metabolites or metabolites that could not be identified. Some studies showed that there was a decrease in serum ammonia, as you would expect, for patients being treated with hepatic disease, but some studies did not. And, finally, there was a transient but significant decrease in hemoglobin and white blood count; however, an increase in pro-inflammatory cytokines, suggesting an imbalance from the anti- to pro-inflammatory situation.

For MARS, again, we identified that there were various benefits, including the removal of protein-bound and water-soluble toxins. It mimics the biologic detoxification process of hepatocytes. And, again, with the hemodialysis component, you get the management of fluid imbalance, electrolyte imbalance, and acid-base imbalance, particularly acidosis.

With MARS we do see some degree of control of glucose and acidosis with lactate acidosis, and we do see the recycling of the toxin-binding proteins. And, finally, we see proven biocompatibility and the fact that this system can be used in conjunction with continuous renal replacement

therapy, providing not only removal of toxins, but also the control of fluid and electrolytes.

However, as with the BioLogic-DT and any extracorporeal therapy, there are the typical catheter complications, including infection, that can ensue. Some patients, as Dr. Topaloglu explained, developed bleeding and thrombocytopenia, and we saw some patients had developed hemodynamic compromise, including hypotension. And, finally, there was fever of unknown origin.

So in our summary for hemoperfusion for hepatic coma, the FDA believes that human clinical evidence shows insufficient evidence showing the benefit for hemoperfusion for hepatic coma. Although some studies did show some benefit, that was not consistently shown. There is inadequate information about the substances that are being removed by all the devices. And, finally, we believe there are significant risks for hemoperfusion in patients with hepatic coma, including bleeding and thrombocytopenia, along with hemodynamic compromise, for which adequate safety provisions or special controls are not yet established.

Therefore, the Panel will be asked to comment on whether they agree that special controls cannot be established to mitigate the risks to health posed by sorbent hemoperfusion devices for the treatment of hepatic coma and that these devices should remain as Class III devices.

Finally, for metabolic disturbances, there is little medical

literature and therefore insufficient evidence and variable efficacy showing the benefit of hemoperfusion for metabolic disturbances. With the limited amount of information, the risks have not been adequately studied, and we believe that special controls cannot be properly established due to the lack of information.

The Panel will therefore be asked to comment on whether they agree that special controls cannot be established to mitigate the risks to health posed by these devices for the treatment of metabolic disturbances and thus that these devices should remain as Class III devices.

If we compare our recommendations for drug overdose and poisoning, shown here in the middle panel, with that for hepatic coma and metabolic disturbances, we believe there is adequate knowledge of the offending substances for most patients who develop drug overdose and poisoning, while this is not always the case and infrequently the case for hepatic coma and metabolic disturbances.

We believe that bench data is available to demonstrate which substances are being removed in patients with drug overdose and poisoning, where it is not always the case for hepatic coma and metabolic disturbances. However, we do believe that bench testing is available to assess the safety for both drug overdose and poisoning as one group, and hepatic coma and metabolic disturbances.

The number of treatments required differ between these two

groups. For drug overdose and poisoning, usually only one therapy is required, about two to three hours, whereas with hepatic coma and metabolic disturbances, usually multiple therapies are required, therefore increasing the risk for exposure to safety and adverse events.

We believe that alternative therapies are generally not that available for patients with drug overdose and poisoning, whereas they may be more available for patients with hepatic coma and metabolic disturbances, which includes the standard medical therapy.

We believe that acceptable safety profiles do exist with mitigated risks for patients with drug overdose and poisoning, but this is not always the case with hepatic coma and metabolic disturbances.

And, finally, we believe that special controls are well defined for patients with drug overdose and poisoning, whereas this is not the case for hepatic coma and metabolic disturbances.

So, in summary, we believe the benefit outweighs the risk for drug overdose and poisoning for the use of hemoperfusion, whereas that is not the case and it is not clearly defined that hemoperfusion provides benefit versus risk as a clear improvement for patients with hepatic coma and metabolic disturbance.

The FDA recommendations, therefore, are to recommend a split classification and the following revision to Section 876.5870: for drug overdose and poisoning, for these to be reclassified for Class II; for hepatic

coma and metabolic disturbances, for these to remain as Class III requiring premarket approval or PMA.

The FDA believes that special controls can be established to permit reclassification of hemoperfusion for the treatment of drug overdose and poisoning to Class II. And the FDA believes that adequate special controls cannot be established to permit reclassification of hemoperfusion for the treatment of hepatic coma and metabolic disturbances and that these devices meet the criteria to remain as Class III devices for these indications.

I want to thank you for listening to our presentations.

DR. TALAMINI: I would like to thank the FDA review team for their presentation.

Does anyone on the Panel have a brief clarifying question for the FDA? Please remember that the Panel may also ask the FDA questions during the Panel deliberations later. If you have a question, please state your name each time you speak, and speak directly into the microphone.

Dr. Afifi.

DR. AFIFI: Abdelmonem Afifi.

I have a question about Slide Number 57. The question is, how does labeling mitigate, for example, platelet loss and clotting and so on and so forth? How does labeling produce mitigation?

DR. SILVERSTEIN: For which risk, please?

DR. AFIFI: For any of those. For example, the first one, platelet

loss or thrombocytopenia.

DR. SILVERSTEIN: Well, not only labeling, but we do have some bench studies. But to focus on the labeling, there are some risks that simply cannot be completely eliminated. So, in the labeling, what you do is you provide warnings to the user, suggesting that platelet loss could occur and patients could develop thrombocytopenia during the therapy. So, it may be that patients with a low amount of platelets may need an infusion or may not be able to receive the therapy. If patients are prone to bleeding, you may want to consider other manipulations to improve their ability to clot. So, there are a variety of recommendations. Labeling generally provides recommendations to the users about what mitigations you can provide if the therapy is required.

DR. AFIFI: Thank you.

DR. TALAMINI: Dr. Dasarathy.

DR. DASARATHY: This is Dasarathy from Cleveland Clinic.

I am just a little confused. What do you mean by the term "bench studies"? Do you mean animal studies, do you mean cell studies, do you mean lab data?

DR. SILVERSTEIN: No, those are laboratory studies. They are not preclinical studies done in animals. Those are studies done with the device on the bench, in which blood can be passed through or a variety of the manipulations can occur. So those are done without the subject, without the

patient, without animals.

DR. TALAMINI: Dr. Sjogren.

DR. SJOGREN: Maria Sjogren.

I have a question. In the packet that we were given, it says that the MARS system has a contraindication, to be used as a bridge to transplantation, a liver transplantation. And my question is, if some of the studies were found with maybe less than 50 people in which the device was indeed useful as a bridge -- or was this so prohibitive that that was not the case at all?

MS. GONZALEZ: The labeling reflects what was presented to FDA during the applications that were made by the company. And so, based on the studies and the data that were presented, we were able to give a labeling of an indication for use. Also, because they are 510(k) devices, they need to be compared to a predicate device, and so the labeling has to reflect the predicate device labeling. If a company were to come in and provide data to show bridge to transplant, for example, then that would be reflected in the labeling. It just wasn't reflected in the application that was submitted for that particular device.

DR. SJOGREN: The question is, was it used anyhow, as we physicians sometimes use devices outside of labeling?

MS. GONZALEZ: Oh, I see. We do not have control over practice of medicine. And so, once devices are in the market and they're

being used by physicians' practices, off-label use in the practice of medicine does occur, and we do not have control over that. We only control the labeling, what's specified in the indications that we clear in our reviews.

DR. SJOGREN: No data available in your review on this specific question?

MS. GONZALEZ: Correct.

DR. SJOGREN: Because, for me, that's a most important thing. I want a bridge to transplant because, with such a critical -- this is a chronic or acute failure. Patients are going to die. So if I can find a way of maintaining them alive for a longer period of time, then my question is did you find any data? I know you don't regulate that, I know it's the label, but was there any data available?

MS. GONZALEZ: No, we did not find any data in the studies. We agree, it would be a great area for research and for a study.

DR. TALAMINI: So if I could just take the privilege of the Chair and ask a further clarifying question. Were there no studies at all addressing bridge to transplant, or were there studies in the review that simply didn't rise to the level of being applicable or usable in the overall review? Or possibility three is that we don't know the answer.

DR. FOY: Good morning. I'm Jonette Foy. I'm a Deputy Director in the Office of Device Evaluation, and bridge to transplant is an indication that we have not cleared through the 510(k) program, so it's really

a discussion that's outside the scope of our discussion today. We're here to talk about the indications that we have previously cleared through the 510(k) program, and those four indications have been put up here for our discussion.

Thank you.

DR. TALAMINI: Thanks.

Dr. Agodoa, did you have a question?

DR. AGODOA: It was already covered.

DR. TALAMINI: Other questions from this side of the room? No.

Dr. Woods.

DR. WOODS: Karen Woods.

Frequently throughout the slide presentations, it was mentioned that the hemoperfusion devices cause a depletion of important nutrient substances and hormones, but there's been no specific discussion of what those things are or how important or clinically significant those particular things are.

Can you give us some additional information and whether or not there would be a requirement? It just says mitigation would be labeling and bench studies, but what sort of labeling are we talking about, recommended replacements or otherwise?

DR. SILVERSTEIN: That's an excellent question and it is, I think, something that we struggle with quite a bit with various filters. Based on the

characterization of the filter, what the pore size is, there are certain substances that are cleared by the filter, and there are certain substances that are retained. We don't always know and sponsors don't always know what those substances are. So what we've done is we've included this as a general labeling, and the sponsors have agreed to this, because we know there are substances that are being lost, various nutrients, vitamins. Some have been studied, some have not been studied, but we can't identify every particular substance. So it's based on the molecular weight of the substance that is allowed to pass through.

So, as a general comment, we don't always know, in the same way that we don't always know what substances accumulate in various diseases and which of those are being cleared. So it's sort of a double-edged sword. We don't know what's being cleared, what the device is allowing to be cleared, that are building up in various conditions. But we also don't know what's passing through, in addition to the substances you desire to be removed.

We just don't have specific bench data. We've requested that information at various times, and we aren't able to always receive specific information about which substances those are. It's just based on the pore size and molecular weight and what we know of the size of substances that exist in the bloodstream.

DR. WOODS: So don't you think that it would be important -- I

mean, me as a clinician, I don't know the molecular weight of a lot of these hormones and substances. But if you know the pore size of the filter, could you not request that they list things in the blood beyond the pore size or below what you know should be important to be concerned about?

DR. SILVERSTEIN: We have requested that, and we sometimes get complete lists, sometimes incomplete lists. The bottom line is, is that you have a multitude of substances which could pass through. If a pore size is X amount and we know -- let's say albumin -- that it's smaller than it, we know it's going to pass through. So we may ask for studies including what are the protein levels before and after the therapy. We can ask for specific substances that are of interest.

But as you can imagine, there are so many substances that you would have to list and do studies for. I don't think that it is something that we can request, that they study every particular substance. There are certain substances and certain diseases where we want to know. I gave you albumin as a typical one because it's an important component of the bloodstream.

And there are certain other proteins: Immunoglobulins. We can ask for that information, some of it just assumed. If the pore size is significantly greater than, let's say, IgG, we know it's going to pass through. So we may ask them to measure the amount of immunoglobulins, let's say, before and after therapy.

But I think that's an issue that we struggle with and we would

like to have more information, but we also understand that's a pretty difficult task to provide that.

MS. GONZALEZ: If I might add, also, it's not just based on the filtration of the filter, the pore size. There are also surface characteristics and surface charge and absorption, especially with charcoal columns. And so it's not just -- sometimes it's not just a clear yes, that that size will be cleared and this one will not. There are some other binding properties of the membranes that are harder to characterize, and we try to characterize them with engineering tests and the bench tests. But as Dr. Silverstein was pointing out, it's hard to characterize everything and label everything.

DR. TALAMINI: Dr. Moxey-Mims.

DR. MOXEY-MIMS: Marva Moxey-Mims, NIDDK.

So I have two questions. One is, in looking at the hemoperfusion for hepatic coma and the risks that are listed for both the BioLogic-DT and the MARS that you list as potentially not being able to mitigate, but when I compare that list to what's on the screen right now for overdose and poisoning, apart from the few reports of studies in humans, really they're the same things that you have listed here for which you said they can be mitigated. So why the differentiation there?

DR. SILVERSTEIN: Yes, I agree with you. The risks for these systems are generally the same, for the most part, let's say, for drug overdose and poisoning and compare it to hepatic coma and metabolic disturbances.

What we're talking about here is whether we should change the classification based on the benefit and risk profile.

So we believe there are two things to go into this. The first thing is patients with drug overdose and poisoning have a different underlying illness than those patients with hepatic coma and metabolic disturbances, and we believe that probably what we're seeing in the literature is a higher degree of risk with patients with hepatic coma and metabolic disturbances because their underlying condition is more significant. So they are more at risk for developing those adverse events.

The second issue is whether the benefit outweighs that risk. And we have found that, with drug overdose and poisoning, the benefit does outweigh the risk, whereas hepatic coma and metabolic disturbance, because of the very, very questionable efficacy as shown in many of the randomized controlled trials and observational studies, we don't see that the benefit outweighs the risk.

So you're correct that many of those risks can be mitigated with special controls, maybe with all of these conditions, but the problem is they're more likely to occur in patients with hepatic coma and metabolic disturbance. And we're not sure that the special controls that can be applied for drug overdose and poisoning will be as beneficial and protect patients as they will for patients with hepatic coma and metabolic disturbance.

DR. MOXEY-MIMS: And my second question has to do with the

whole metabolic disturbance aspect, for which you said there was no data found in the literature. And I'm wondering, is it because that term is just too broad? I mean, what specific metabolic disturbances? Perhaps it ought to be narrower rather than just looking for metabolic disturbance. There are so many things. One of the slides lists some specific ones, and I'm wondering, when the search was done, was it done looking at those specific disturbances or just the generic term "metabolic disturbance"?

DR. SILVERSTEIN: That's a very good point, and that's something that came up in our discussions early on as we were going through our review. I found the term to be very, very vague. And exactly, myself, that's the terminology that has come through from the original classification, so we're bound to review it in that way.

Now, to your question about whether we looked at specific disturbances, I did do that. I looked at patients with thyroid disease and patients with diabetes. And, again, we really weren't finding anything.

So there are two possibilities. Either hemoperfusion is simply not being performed for a variety of these "metabolic disturbances" or it's not being reported. It's not clear. So we're left with a general term. And so we tried various search strategies, including what Dr. Topaloglu showed herself. We actually did our reviews and our searches separately. So what we did is we put in search terms, but then we dug a little bit deeper than that, and that's about all we could find.

DR. TOPALOGLU: I just would also like to add that, in our search term, we didn't restrict indications, so there was no restriction for indication. We didn't use search terms specifying indications so that we can include all kinds of indications. And looking at reviewing the papers, there were only, I think, two or three papers which were also mentioned in Dr. Silverstein's presentation, small studies and case reports on metabolic disturbances.

DR. TALAMINI: Dr. Schwaitzberg.

DR. SCHWAITZBERG: Steve Schwaitzberg.

In looking at Slides 41 through 46 and similar numbers in the 60s, as I look at the dates of the literature, I'm struck by the fact that all of the data on charcoal hemoperfusion is very old, more than 15 years. It seems like nobody's writing about it and nobody's doing it, because people are writing a paper about everything every day.

I guess this is a technical question. You split this, and taking hepatic coma and metabolic disturbances as a split, do we have the option of making recommendations for charcoal hemoperfusion different from, say, BioLogic-DT or different from MARS? Is that within the purview of the Panel, or is this a winner-take-all one big lump?

And I'm disturbed by that. You're shaking your head no. I'm bothered by that because we're lumping data from the 1980s with current data, and we may choose to find some of the more recent studies and recent

techniques to be more favorable. But when you throw in the old data, you're throwing a lot of noise into it, which prevents us from making our best recommendations.

DR. SILVERSTEIN: I'll tackle the last question first, about whether we can parse out therapy with this particular therapy or device or not. We can't parse it out; it all comes together. The only other comment I want to make -- you're right, about the use of hemoperfusion. As a clinician, myself, and various other clinicians, I think they can tell you that the use of hemoperfusion is certainly declining for a variety of conditions, especially for drug overdose and poisoning.

That said, we have a lot of solid data from the 1970s and 1980s supporting its use. There was a recent study that came out a few years ago that looked at the use of hemoperfusion for a variety of conditions, including drug overdose and poisoning, and it's certainly declining over the years. So the reason we're seeing less published is, number one, we have good information for drug overdose and poisoning. So for those particular indications, there is a lot of historical data that's very, very useful. And the second thing is that we're seeing it used much less frequently.

So, for hepatic coma and metabolic disturbances, especially for hepatic coma, I think that's a little bit different. But we're not able to parse out that we're going to reclassify for BioLogic-DT and not for MARS. We're not able to do that.

DR. NEULAND: Hi, I'm Carolyn Neuland. I'm the Chief of the Renal Devices Branch that reviews these devices.

One thing I want to point out is that we're looking at a class. These are types of devices, and they're called hemoperfusion. We can't break individual devices out at this time because they were all found equivalent to each other. So if something comes in and it's different, we look at the technology and we look at the indications for use and we say, is that substantially equivalent? If it's not, it becomes a Class III device; we find it not equivalent. Those might be in a different group, but at this time we found these equivalent.

DR. SCHWAITZBERG: So if I understand you, it's the chain going backwards of how things were originally approved as substantially equivalent to things that are now known to be not effective.

DR. NEULAND: Or not used.

DR. SCHWAITZBERG: Or not used.

DR. NEULAND: Yes. We think these were as safe and as effective as what was on the market. They might be better. And they were pre-amendment devices, remember, to begin with. This classification was out there before 1976 and these were devices on the market.

DR. SCHWAITZBERG: Yes, they may have been hoist by their own petard there.

DR. TALAMINI: Dr. Woods.

DR. WOODS: Just a question as a point of clarification for my understanding on the classification, so with regard to the hepatic coma indication, so these devices are currently Class III. When they came to market, were they presented to FDA as a 510(k) or a PMA? And if we classify them, if FDA classifies them now continuing as a Class III, will the existing devices be required to present a new PMA, or will they be grandfathered in on their -- whatever status they had before?

MS. GONZALEZ: They were classified as Class III from the original classification panel in 1978, but the PMA was never called. So they always were regulated and reviewed by FDA under 510(k)s. So when a manufacturer came in with a new device, they submitted a 510(k), they compared themselves to something already on the market, and there they went and got their clearance. And we showed that list of clearances that we had, about ten 510(k)s cleared.

Once the reclassification comes through, depending on what's decided, if some portion of a device -- some uses become Class III, then any device that is going to be in the market or that's currently in the market, to stay in the market they need to submit a PMA. We'll put out a date by which time the PMA needs to be submitted, and the manufacturer will have to submit a PMA, and once the PMA is approved, they can remain in the market. But if they don't submit a PMA or if the PMA is not approved, then they have to come off the market.

DR. WOODS: Okay. Just so I understand, black and white, right now they're all 510(k)s.

MS. GONZALEZ: Correct.

DR. WOODS: If it goes through as a Class III, every one of them will come back to you with a PMA if they want to stay on the market.

MS. GONZALEZ: Correct.

DR. WOODS: Okay.

MS. GONZALEZ: And that is a manufacturer's choice to submit a PMA, if they want to, for their device. Otherwise they can desist marketing.

DR. WOODS: Okay.

DR. TALAMINI: Dr. Moxey-Mims, did you have a further question?

DR. MOXEY-MIMS: No.

DR. TALAMINI: Dr. Schwaitzberg.

DR. SCHWAITZBERG: Just to be perfectly clear, the PMA would only be for the hepatic coma indication? So they would be able to be on the market for the indications that would be found to be compatible?

DR. NEULAND: That's correct. I was just going to clarify that point. So if they have both or all indications, then those indications, one would have to come out of their labeling until they come in with a PMA.

DR. TALAMINI: Dr. Dasarathy.

DR. DASARATHY: This is Dasarathy from Cleveland.

I'm still not sure. You're saying the use has declined or the use is the same or is increasing based only on published literature. You're not basing it on sales of products. So we don't really know whether they're being used or they're not being used, except that you're tracking --

DR. SILVERSTEIN: For drug overdose and poisoning, the one study that I can find -- I can get you the specific reference for that -- showed that the use for drug overdose and poisoning has declined over the years. It declined by about 50%. For hepatic coma, I did not find literature that specifically stated how much uses there are. We're not talking about devices that are out there. We're talking about the number of therapies provided.

For drug overdose and poisoning, it has definitely declined. If you look at it from 1986 to 2005 and 2005 and after, just the rate of use per year has significantly declined. Now, the reasons for that, I think, are most likely that hemodialysis, now we have different types of filters, so we can use it. I think also there is an element of the fact that since fewer people are being trained on it, fewer people are using it, so that becomes sort of a self-fulfilling prophecy. But it's still being used, it's still available, and it's still efficacious. It's just that the use of it in clinical practice has declined for a variety of other reasons.

DR. DASARATHY: But it looks like, to me, the MARS is being used much, much more.

DR. SILVERSTEIN: It's for a different indication. The use I was

talking about, that you had asked about, was for drug overdose and poisoning. For hepatic coma, as I mentioned, I didn't find particular references that showed how much uses there were. But it seems to be, based on the literature, that there is greater use of hemoperfusion for hepatic coma than there had been in the past.

DR. TALAMINI: Dr. Agodoa.

DR. AGODOA: Larry Agodoa, NIH.

If these devices are not being used very much for drug overdose and poisoning anymore, why bother to reclassify them?

DR. SILVERSTEIN: We're being required to go through this process. So the devices that were Class III and now being reviewed under the 510(k) process, we are required to put this forth to a panel for reclassification. So this was not a decision based on clinical use, upon what's out in the market. This is a requirement from Congress, under FDASIA, to go through this process. So we're bringing it to you experts to ensure that this is a process that we have fully vetted out.

DR. TALAMINI: Any further questions of clarification from the Panel?

Yes, Dr. Simon.

DR. SIMON: I know we're not here to discuss hemodialysis, but if we could just spend 10 seconds just to model sort of the thinking for the Panel, because perhaps that could inform the thinking in terms of our

mandate. So this is for any member. So hemodialysis, those devices, membranes dialyzers, they're all Class II; is that correct?

MS. GONZALEZ: That's correct; they're Class II.

DR. SIMON: Were they ever Class III?

MS. GONZALEZ: Some dialyzers were Class III, the high-flux dialyzers that had a higher cutoff were Class III, and they were down-classified to Class II.

DR. SIMON: All right. So now everything in dialysis, to just sort of be a lumper, is Class II essentially.

MS. GONZALEZ: Correct.

DR. SIMON: And if a new device comes on the market, it's essentially Class II until proven otherwise or the FDA feels it's mandated Class III. And our mandate is essentially to split this categorization on hemoperfusion into Class II or Class III, I mean, to sort of summarize and give an overall context of things.

MS. GONZALEZ: We're proposing a split. You can choose to keep --

DR. SIMON: Of course.

MS. GONZALEZ: -- all the devices in Class III, keep all -- change all the devices to Class II, or do a split as per use, is what we're proposing.

DR. SIMON: Okay. I mean, I don't want to speak for everyone's thinking, but it seems that hemodialysis serves as an excellent model in terms

of how to approach this.

DR. TALAMINI: So this is probably a good time for a break. Are there any other clarification questions before we take that break?

(No response.)

DR. TALAMINI: Hearing none, we'll now take a 10-minute break. Panel members, please do not discuss or contact anyone about the meeting topic during the break. This includes discussion amongst yourselves or with any members inside or outside of the audience. We will resume at, let's say, 9:55.

Thank you.

(Off the record.)

(On the record.)

DR. TALAMINI: So we'll now reconvene following the break.

Dr. Eric Marks has now joined us on the Panel. Dr. Marks, if you could please formally introduce yourself to the Panel, as we have with everybody else. If you could push the silver button on the microphone and speak directly.

DR. MARKS: Okay. I'm Eric Marks, Professor of Medicine at the Uniformed Services University, and a clinical nephrologist.

DR. TALAMINI: Thank you, Dr. Marks.

We will now proceed with the Open Public Hearing portion of the meeting. Public attendees are given an opportunity to address the Panel,

to present data, information, or views relevant to the meeting agenda.

Ms. Craig will now read the Open Public Hearing disclosure process statement.

MS. CRAIG: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with any company or group that may be affected by the topics of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at this meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

DR. TALAMINI: We will now hear from our first scheduled Open Public Hearing speaker. Each speaker will be given five minutes to address the Panel. Once you have been asked to approach the podium, please be sure to state your name, company, and any affiliation you may have

with the entities discussed today. And in the interest of time, we will unfortunately need to cut any public speakers off at five minutes, so be warned.

So if we could have our first public speaker. I think, Dr. Yttri. Is Dr. Yttri first?

DR. YTTRI: Thank you. They didn't get this in order, so we'll choose it ourselves.

I am Dr. Jennifer Yttri, and I thank you for the opportunity to speak today on behalf of the National Research Center for Women and Families. The Center does not take funding from device manufacturers, and therefore, I have no conflict of interest today.

The Center uses research-based information to encourage new, more effective treatments, programs, and policies that promote public health. We conduct research, publish our findings in medical journals, and provide unbiased and understandable information to patients, health professionals, and policymakers through CMEs, briefings, testimonies, and other reports. Our major focus is the quality of medical care and medical products, and our president is on the board of directors of two nonprofit organizations dedicated to helping the FDA obtain the resources it needs: the Reagan-Udall Foundation and the Alliance for a Stronger FDA.

There are a number of reasons why the hemoperfusion systems discussed today should remain Class III devices requiring a PMA. These

devices are intended to reduce mortality from poisoning or drug overdose, for instance. This lifesaving indication deserves a Class III designation and a PMA requirement to prove safety and effectiveness. That is absolutely crucial because there is not clear evidence providing reasonable assurance that hemoperfusion systems are safe or effective for this and other indications.

Based on the risk information provided by the FDA and confirmed by a device manufacturer in a comment to the FDA docket, the proposed special controls will fail to provide appropriate effectiveness information; lack of biocompatibility, unclear labeling, and poor removal of toxins, all reported in complaints to device manufacturers, have been identified as significant risks. Bench testing of absorption has not been proven to correlate with important patient outcomes such as survival. The only way to get this information would be through the PMA process, requiring clinical testing.

Some of the risks on the long list provided by the FDA are similar to other devices used for the same indication. But how do the hemoperfusion systems compare to these other devices? There's limited scientific evidence comparing hemoperfusion to other standard treatments for drug overdose or poisoning. Hemodialysis seems to be preferred, as it costs less, is better tolerated by patients, and works for a larger range of toxins than hemoperfusion systems. There is insufficient scientific evidence that hemoperfusion is as safe or effective as, for instance, hemodialysis.

Hemoperfusion systems have not been proven to save lives or reduce morbidity. And yet, that is the goal of these devices. The effectiveness in removing toxins from the body seems to vary depending on the device, treatment duration, and the target drugs.

In conclusion, we don't know how well these devices work for any overdose, and their efficacy is especially questionable when used to treat hepatic coma or metabolic disturbances. In all of these cases, hemoperfusion is being used as a lifesaving treatment. The proposed special controls will not be adequate to ensure the safety and benefit of patients requiring hemoperfusion. Bench testing of functionality and drug absorption does not reflect patient survival. Labeling approved for these devices by the FDA has already proven ineffective at providing safety and use information to patients and medical professionals. Biocompatibility and performance data are no substitute for clinical testing.

Please vote to retain the Class III classification for sorbent hemoperfusion systems for all indications. Our goal today is to make sure that these lifesaving devices are safe and effective.

Thank you.

DR. TALAMINI: Thank you.

Is there a representative from Gambro here to speak publicly?

(No response.)

DR. TALAMINI: If not, are there any other public speakers?

Yes, sir.

DR. HAMILTON: Good morning. I thank you for the opportunity to address the Panel this morning. My name is Leroy Leslie Hamilton. I have a Ph.D. from Case Western Reserve University in biomedical engineering.

Relevant to the proceedings here is that I was an FDA employee. I worked in the Bureau of Medical Devices from 1974 to 1976. In fact, I was the executive secretary for the Radiological Devices Classification Panel, and I was also associate executive secretary for the Gastroenterology-Urology Panel.

A very interesting experience during that time was that I was present at the meeting of the subcommittee that dealt with hemodialysis devices and had the privilege of observing Dr. Koff (ph.) and Dr. Friedman from Downstate, and an engineer from New York University, I think -- Columbia University -- as they discussed the classification for those devices. And if time permits, I'd like to tell an anecdote about that experience.

The reason I'm here today is to bring your attention to what I consider to be a serious logical flaw in the logic diagram that was presented to the Panel earlier by an FDA speaker. That slide is on your screen now, and this is intended to be a logic diagram illustrating how the answers to the various questions lead to the classification for the device.

The serious flaw that I point out is the following: Class I, which

appears down at the bottom, can be achieved by either of two routes. The first initial question is, are general controls sufficient to provide reasonable assurance of the safety and effectiveness of the device? And if the answer is yes, it is eligible for Class I. If the answer to that is no, then it would never be eligible for Class I under any circumstances, regardless of the answers to the other questions. However, the diagram, if you follow it to the right, if you answer no to the first question, no to the second question, no to the third question, no to the fourth question, you end up as Class I. That I consider to be a serious logical flaw.

Now, some people would say I'm making a mountain out of a molehill. That's not the case. I've been talking with FDA people, trying to engage in a meaningful conversation about a related issue on this subject for 16 months, and no one wants to talk to me. It's amazing that I'm actually given permission to speak at this meeting.

There is a history behind this. I won't go into the details of it except to say that the FDA has a form, 3429, called a classification questionnaire. Last year I discovered that it had a serious logical flaw, not unlike the one that I just described to you. But in that case it led to Class III for devices that didn't satisfy the definition of Class III in the law.

I submitted a citizen petition in July. That petition was granted finally in March of 2013. That petition also led to modification of the classification questionnaire which strangely enough became effective in

July 2012. It's almost as if the Agency turned the clock back. They didn't turn the clock back. The reason that they made the change in the classification questionnaire -- and they deleted all of the logical column. That questionnaire no longer leads to any class. You answer the questions, but it never tells you whether it's Class I, Class II, or Class III. They omitted the column that indicates the classes, and that was a result of an earlier citizen petition that I submitted in April of 2012.

Now, I bring these to your attention because I think it's important --

DR. TALAMINI: Thirty seconds, sir.

DR. HAMILTON: -- for Advisory Committees like this one to appreciate the fact that you are fed information by the FDA, you're spoon fed, and all you get is what they tell you. They don't tell you what they don't tell you, and I'm here to tell you that there are things you really need to know.

DR. TALAMINI: Time is up, sir.

DR. HAMILTON: Well, thank you very much for your attention, and if there are any questions, I'd be happy to answer them.

DR. TALAMINI: Thank you.

Does anyone else wish to address the Panel at this time? If so, please come forward to the podium, state your name, affiliation, and indicate your financial interest.

(No response.)

DR. TALAMINI: Seeing none, does the Panel have any questions for the Open Public Hearing speakers?

(No response.)

DR. TALAMINI: No questions. I now pronounce this portion of the Open Public Hearing to be officially closed. We will proceed with today's agenda. We'll now begin the Panel deliberations.

Although this portion is open to public observers, public attendees may not participate except at the specific request of the Panel Chair. Additionally, we request that all persons who are asked to speak, to identify themselves each time. This helps the transcriptionist identify the speakers.

So Panel members, you've heard the FDA presentation and you, I'm sure, by now understand the paradigm or the proposal that they're putting forward. This is now our opportunity, as a Panel, to discuss publicly whether we agree with that direction, whether we have further questions or wish to deliberate amongst ourselves further regarding their proposal, and it's also our opportunity to ask the FDA further detailed questions. Once we close this portion, we will begin to address formally the questions that the FDA has put before the Panel.

So with that in mind, I would ask the Panel members to make comment on the literature review, the proposal, and I might ask our

nephrology members to potentially lead that discussion with respect to the direction that the FDA is taking us.

Dr. Faulx.

DR. FAULX: Hi. I have a question that maybe the nephrologists can answer, just to clarify, because it's not my area. But with toxin overdose, is generally standard of care dialysis now? So are we looking at comparing dialysis versus hemoperfusion, because you were talking about the FDA presenting about other therapy that's more standard than hemoperfusion? So not really understanding that. Is there good data on dialysis that we should know about versus hemoperfusion?

DR. FISHER: This is Ben Fisher, FDA.

I appreciate that, and I'll have one of my nephrologists answer this question, but I really would like to focus on the hemoperfusion. I don't want to get into a big comparison of what's going on with hemodialysis. We really need to focus on the hemoperfusion and the intended uses that we're putting forward. We seem to keep going over to the hemodialysis side, and I'd like to kind of stay focused on the hemoperfusion, if we can.

DR. FAULX: I guess my question was just because there is so little data that we have and so I just didn't -- I guess that was just not -- if there are not large randomized controlled trials, more than 50 patients, is it really, I guess, something where we want to put this into Class II versus Class III? And that was my only question.

DR. TOPALOGLU: As far as the literature review, we included all the other therapies as standard of medical therapy or specific therapies like other devices and so on. But the standard medical therapy varies, so we looked at them as compared to a standard medical therapy. But we didn't go into detail, and it would be difficult, I guess, to tear that apart from each other.

DR. TALAMINI: Dr. Agodoa.

DR. AGODOA: Larry Agodoa, NIH.

I am, I guess, stuck again on this Slide 57, when you have the risks and mitigation. As I understand it, the mitigation is supposed to -- I'm not quite sure. Maybe other Panel members can explain this a little bit better to me, how labeling and bench studies can mitigate these risks.

DR. TALAMINI: I would ask our FDA representative, perhaps, if you could further clarify that issue in that slide for us. I think it was Slide 57.

DR. SILVERSTEIN: I'm just in the process of trying to obtain it, but let me just address it. I want to take Dr. Fisher's point a little bit further. It's an interesting discussion, whether or not hemodialysis or hemoperfusion is better, depending upon what the exposure may be.

But the point of our Panel meeting today -- and it's a very, very good question and it's a question that comes up clinically all the time. But the point of the Panel meeting today is not to compare the two. It's to look at the evidence regarding drug overdose and poisoning and the use of

hemoperfusion and whether the evidence shows that there is a benefit and that that benefit -- and then compare it to the risks and then to discuss whether these devices should be classified as Class II or Class III.

So it's very, very clear that there is not as much evidence currently as we find from the past. But the past evidence, we believe, is clear that depending upon the exposure, if the exposure can be identified, that hemoperfusion provides a benefit with a minimal amount of risk.

Now, the question then comes up about this list of -- and I'm having a hard time seeing that, so I'm going to read it off the computer here. There are risks associated with the use of any device, and some of those risks can be minor and some of those risks can be significant. What we ask manufacturers to do is to mitigate those risks as much as possible by providing some evidence either in bench testing, in their device design, or in their labeling. That doesn't mean that the risk is going to be completely eliminated; it's going to be mitigated.

And that's where we believe special controls can be applied, because special controls will allow you to make certain recommendations in the labeling to reduce the risk to the patient. It doesn't eliminate the risk; it just reduces the risk. Some bench studies do provide some supportive data, but as one of the Panel members discussed before and made a very, very important comment, it's not clinical data; it's bench studies.

So what we have to do then is refer to the literature and assess

whether the adverse events reported in the literature tell us that the risk cannot be mitigated by special controls. The literature for hemoperfusion for drug overdose and poisoning -- albeit, it's literature from the 1980s and 1970s and maybe a little bit from the 1990s -- tells us that the reported adverse events were very, very minimal, they were significantly outweighed by the benefits, and whatever adverse events occurred, we believe, can be addressed by bench studies, by device design and by labeling. It doesn't mean they're going to be eliminated; it just means they're going to be significantly reduced.

In comparison, just to move over to the issue of hepatic coma, we believe, because of the underlying condition of those patients, some of those risks are relatively similar in theory. But because those patients have a particular risk because of their underlying disease, they're more vulnerable. We didn't believe those can be addressed by special controls.

Is there something particular on this list that is of a concern that it cannot be mitigated by a special control?

DR. TALAMINI: You know, perhaps you could give us an example. So platelets. You label the device, that there's a risk of platelets. The mitigation action might be monitoring platelet levels over a period.

DR. SILVERSTEIN: Yes.

DR. TALAMINI: Is that correct?

DR. SILVERSTEIN: I can only give you an example because I

can't refer to a specific manufacturer's labeling. But, for example, as a reviewer, what I would look for is it's acceptable to me that there may be some risks associated with a device for a particular indication. What you want to look for as a reviewer are those risks, can they be mitigated by certain features in the applications?

So number one, let's say for labeling. I would require, for certain types of devices -- this is in general, this is nothing specific -- that for a platelet count below a certain value, that the therapy is contraindicated. That would be one way to do it. Another way to address that may be that for patients who have a significant risk of bleeding even in the absence of thrombocytopenia, that certain clotting factors can be measured and that, again, there may be a contraindication of those clotting factors indicating an enhanced risk for bleeding.

So, again, it's not that we can eliminate the risk completely, and it's not that we can with the labeling, therefore, eliminate that risk. It's just that the labeling is information to the user, to the physician, to any clinician, to a nurse who is running that therapy -- all of the above -- that if these things occur, there may be certain contraindications. For every device I have reviewed, there are always contraindications. And very often the FDA may require an expansion of that list because we believe that, in their labeling, which is in their labeling, the contraindications can reduce the risk for certain at-risk vulnerable populations.

DR. TALAMINI: So let me -- yeah, I'm sorry.

MS. CHAUHAN: Go ahead, I'll wait.

DR. TALAMINI: To try and broaden the discussion a little bit, let me push the Panel and ask Panel members. You've heard the proposal that the split, and that for the two indications, this would move to Class II. Are there Panel members that feel that, for all indications, this should move to Class II and that special controls be applied? Is there a Panel member that would want to speak for that potential or push in that direction or ask a question about that direction?

Dr. Schwaitzberg.

MS. CHAUHAN: That's -- oh, I'm sorry. That's sort of where my question was. Cynthia Chauhan, Patient Rep.

Historically, are there other devices that have this split classification, and how has that worked? I'm concerned. Somewhere in my pre-meeting reading, there was a very brief comment about the potential for abusive use, using the Class II to go ahead and do the Class III things. And so that's my question.

DR. SILVERSTEIN: The law is a relatively recent law, so I am not aware of any particular split classifications. There may be. And maybe there are some other FDA personnel -- I believe there have been, but I can't identify particular ones. I can ask for my colleagues to maybe provide that information.

As far as your second question, you had asked about --

MS. CHAUHAN: Once you do split the classification, how do you control the split?

DR. SILVERSTEIN: Well, what would happen is, is that the hemoperfusion for drug overdose and poisoning becomes Class II, and therefore, the special controls are then enabled to reduce the risk. But the hemoperfusion for hepatic coma would remain as Class III, as is, requiring PMA, premarket approval.

So it's simply a process by which the FDA, moving forward, would then classify these devices if a similar device comes in for review. It doesn't necessarily change the way the devices are being used as of today. It's a way they're being classified and the way they're going to be reviewed in the future.

DR. TALAMINI: Does someone else from the FDA have further comment?

DR. FISHER: Yeah, I'd just like to make a comment that with the special controls, we look at the benefit/risk here. Our suggestion is that we break this into the four indications, so that's why we're looking at it this way. We think that we've identified those risks, and we talked about special controls. If these special controls get put into place, this is something that all manufacturers would have to comply with. So, that's one point.

Going back to labeling, I just want to touch on labeling real

quick. We're at a little bit of a limitation because, when we're clearing a 510(k), we look at these devices for the specific indication for which they come in for. So, we look at those. And I think that what Dr. Silverstein is saying, as we identify some risks, we try to get some of that into the labeling. But one of the things that we don't want to do is have the labeling so broad that it gets outside of the information that we have. So, that's kind of how we use the labeling to help mitigate some of these risks. The special controls are a different step that we're trying to take for us to put into place. It will actually help us with the labeling, also.

DR. TALAMINI: Further comment from the FDA? It looks like the rulebook is out.

(Laughter.)

MS. SHULMAN: Hi. Marjorie Shulman.

There are a number of regulations that are split. For example, the colonic irrigation system is split between Class II when the device is intended for colon cleansing when medically indicated, such as before a radiological endoscopic examination, or Class III premarket approval when the device is intended for other uses, including colon cleansing routinely for general well-being. So, there are a number of regulations that are split, either based on indication for use or the technology of the device.

DR. TALAMINI: Thank you.

Dr. Schwaitzberg.

DR. SCHWAITZBERG: So to address your specific question, Dr. Talamini, in view of the split indications, when you look at 21 C.F.R. 860.7(e)(1), it says there's reasonable assurance that the device is effective when it can be determined, based upon valid scientific evidence. And in view of the profiles of the potential risks, there are risks and we're worried about how well these are mitigated. For the two indications that they would propose to put into Class III, there just simply isn't enough data, particularly when you can't sub-split the different types of sorbent devices, which was my earlier question. If you could split them down, you could go, well, there's really no evidence in charcoal hemoperfusion and that lack of evidence is dragging the whole class down, if you view it in terms of these regulations.

So, I think it is reasonable, based on the differences in data. It's not to say that it's unsafe. There's just no data to suggest that it is safe, in view of the regulations we're being asked to consider.

DR. TALAMINI: Thank you, Steve.

Other thoughts or comments? Yes.

DR. FISHER: I would like to, if we could bring -- Doug, if you could bring the slide back up that has the comparison to the drug overdose compared to the metabolic disturbances. So what we've done is we've put together a summary slide that -- I understand the concern about having one specific device that may be dragging down a group of devices, but we've chosen to look at these four indications. So what we've done is to break this

down into the two indications that we believe we can mitigate and how that compares to the other two groups. So I just offer it up, and if you have some specific questions, maybe we could address them on that.

DR. TALAMINI: Dr. Marks.

DR. MARKS: Two questions. One of them deals with what you can put in a label. In looking at what they have here, can you label this in such a way that it says that this device is not indicated for the use of, as a part of that? Because you're talking about clarification of data in terms of what drugs, for example. I'm looking at these for about perfusion, because my concern from having used these devices and watched them over a period of time is that the data is collected in a controlled fashion around centers that have experience with this. Having them out for general use, anybody who has the ability to provide extracorporeal therapy can have access to these devices to do them.

And so the labeling, in my mind, would have to be restricted from the point of you saying these devices are not for use in, for example, hepatic coma and certain metabolic disorders and are only indicated for the use for the following indications, because otherwise I think your point is well taken. You have no control. It's really a privileging issue, in most places, privilege on the basis of the ability to provide extracorporeal therapy, not the specific aspects of the therapy that might include.

DR. FISHER: Well, we can recommend -- we can require it in

the labeling, but if we strongly recommend and we provide good enough evidence, the sponsors usually comply to say that there are certain contraindications, and we can say that the safety and effectiveness for that device for that particular indication is not available. But we can list contraindications.

And at least in my personal experience -- it's certainly not the FDA experience -- if you can provide a rational argument that you believe that it is not safe in a patient, for a certain condition, with a certain underlying condition, a contraindication, the sponsors usually do comply with that. Again, they are not required to make the labeling changes. These are just certain -- this is information that we are suggesting that they put in the labeling. But if a reasonable argument can be made, it is usually complied with.

DR. TALAMINI: Ms. Shulman, did you have further --

MS. SHULMAN: Yeah, thank you. Marjorie Shulman. I just want to clarify something, too.

We can have the labeling of contraindications, warnings, and precautions, but we also have the ability to do a substantial equivalence letter that would say they would have to put that in their labeling, to say the safety and effectiveness has not yet been shown. For example, we do it with biliary stents used in the cardiovascular system. It says that the safety and effectiveness for this indication has not been established. So we do have --

from another law, it gave us a firmer way to put this kind of a contraindication into the labeling for an SE with limitations.

DR. TALAMINI: Dr. Marks, did you have a second question?

DR. MARKS: No.

DR. TALAMINI: Dr. Schulman.

DR. SCHULMAN: I think the use of hemoperfusion has a niche in the care of patients with the poisoning or drug overdose and particularly in drugs that are highly protein bound, for instance. And so I think that certainly giving approval to the systems for drug overdose or poisoning should be moved down to a Class II.

DR. TALAMINI: Let's see. Going in order, Dr. Dasarathy, I think.

DR. DASARATHY: We heard all of the data on the published literature from Dr. Silverstein, who has done a pretty thorough evaluation of everything. But when these devices were approved, did the FDA ask the manufacturers to collect postmarketing data, and is that data available? Because that will probably be a much more objective measure because, as Doug said, each of us has our own biases. I tend to report positive reports. I don't generally report negative things, not because I don't want to report them, because I can't get anybody to accept them. So I am not necessarily sure, looking at only the published literature, if this device has that kind of data.

The follow-up question to that is, there is this thing about

splitting the indications. Now, if we go back to this -- you know, I'm not an expert on poisoning; I'm an expert on liver failure. But it seems that there are some drugs which can be removed by the hemoperfusion systems, whereas others are not preferentially removed by the hemoperfusion system. So should the labeling include that this works for these poisons as we know them today? For the others, either there is insufficient data or it does not work. Can you clarify that, if it is at all possible?

DR. NEULAND: Well, first to address your question related to postmarket studies. When these devices were put on the market -- it's been quite a while ago, you know, the late '70s -- there were no postmarketing requirements that were easy to put into a 510(k). So we've never asked for postmarketing studies, and it was not something that we could force a company to do based on the 510(k) process, the substantial equivalence. If the predicate didn't do it, they probably didn't have to do it, unless we had a good scientific basis for something different. There are certain things in place now through special controls that we might be able to ask for a postmarket study. We also can do it in any PMA. All of the PMAs, they're approved one at a time, and you can have all kinds of postmarketing requirements in those.

DR. DASARATHY: So if you ask for a data capture by the manufacturer under special controls versus a PMA, I'm not sure how it would be different in terms of --

DR. NEULAND: Right.

DR. DASARATHY: -- having them available.

DR. NEULAND: Right. And maybe Margie can answer that a little bit. But if they have a special control, we can have certain requirements that we ask them to do, but it might be somewhat limited, again, because we're in the world of 510(k). And PMA, you're looking at it as a standalone device. Is it safe and is it effective for the indicated use? And we can do postmarket data to support the various things that we think are still unknown at the time that we approve it.

The 510(k) and special control means you have to do a postmarket study, you have to do a registry. You can name something, I guess, but that's something you'd have to talk about, whether that would be a different special control than something we have here. You can make that recommendation, and then we can decide and talk about how we would implement something like that.

Your second question. Now, I did want to go on to that and that was, could you tell in the labeling -- have them say exactly what they removed? And I think that is one of our recommendations, a special control to have companies list the drugs that they can remove in their labeling. And if you want to say they've proven they can't remove certain ones, you could put that in, because that is one of our requested special controls for the drug overdose and poisoning. Again, for hepatic coma, we don't really know everything we're removing, so that would be harder to do.

DR. TALAMINI: Thanks.

Dr. Agodoa, a question?

DR. AGODOA: Larry Agodoa, NIH.

As I understand it, to move from Class III to Class II, there are two things we need to show. One is effectiveness and a special control. The literature that you presented with both poisoning and drug overdose, I'm having difficulty actually seeing the effectiveness in this. The paraquat one, which has almost 100% removal at 15 minutes, but we don't have any clinical data about how the patients fared; 54 patients. The Peng 2004 data with the SMT showed a significantly lower mortality. But the multiple ones in 1983, the mortality rate was 22%. Then the drug overdose, again, we don't really see clear benefit. The acetaminophen data in 1974 showed no survival benefit.

So I'm having trouble, from your side of the literature, seeing the clinical benefit from both poisoning and drug overdose. Maybe you can clarify that for me a little bit. That's Slide 37 and 38.

DR. TOPALOGLU: First of all, we do acknowledge that the evidence is limited for poisoning and drug overdose. So here I briefly try to summarize the strengths and limitations of those studies included for poisoning and drug overdose. A strength, a total of -- in these included studies, a total of 609 patients were included, and almost half of them were treated with hemoperfusion. One study had a comparison group where they

compared outcomes to standard of medical therapy, and there were two prospective studies. But as you mention, there are limitations. There was only one small RCT, which had 16 patients. And in the majority of the studies, there were no comparison groups.

When we look at the literature, what they mention there is hemoperfusion treatment comes as a last resort, so the patients are in severe medical condition. So that's a selection bias for the patients, so the outcomes might be not so favorable for these severely ill patients.

DR. TALAMINI: So let's just hear more from the FDA. Yes.

DR. SILVERSTEIN: Just a couple more additional comments. First of all, it depends upon the particular exposure, whether or not hemoperfusion is going to provide the benefit. So it depends. Like we mentioned, paraquat, acetaminophen, there are some studies that don't show a tremendous benefit, but I think it's also important to remember it is the time of exposure and the time to get the therapies initiated.

So if you do a study in which you show that patients with acetaminophen overdose were treated eight hours later, just for example, with hemoperfusion, you're not going to see a great benefit. So the studies have shown -- there were a couple of the smaller studies that have shown that early institution of hemoperfusion for patients with certain types of overdose did show benefit versus standard therapy.

The other important information is, again, we have to bring in

safety. The safety data from all of those studies have shown very, very few safety concerns for patients who were receiving hemoperfusion.

And, finally, I do want to add the fact that there really -- for many poisonings, there is no alternative therapy. Sometimes it just takes time. So the outcome sometimes depends upon the amount of overdose, the time of overdose, and the underlying condition of the patient.

But without alternative therapies, with very, very few adverse events reported, and with the caveat that early therapy has shown to provide some benefit -- it may not be a tremendous benefit, but it's versus not being able to do anything -- I think that we believe that because of the low risk and some degree of benefit with certain types of therapy, with certain types of clinical scenarios, we do believe the benefit significantly outweighs the risk.

But I'm not going to disagree with your point that the literature doesn't show a tremendous benefit for hemoperfusion with, let's say, acetaminophen versus standard medical therapy. But, again, the devil lies in the details.

And, again, I do want to emphasize again that we focus on safety as much as anything else we focus on, and the safety for hemoperfusion for patients with drug overdose and poisoning has been established to be -- these have been established to be very, very safe therapies. So I hope that provides some clarification.

DR. TALAMINI: Yes, Dr. Fisher.

DR. FISHER: Ben Fisher.

Once again, I would caution about looking at very specific indications, paraquat versus acetaminophen, or getting into comparisons along those lines. You know, once again we're looking at these as kind of general indications.

But I wanted to go back to a couple things that dealt with the special controls as well as what happens when a device may go to Class III and a call for a PMA, and that is that if we know -- you know, one is how much information do we have? So if something were to go to Class III, we would ask for that information. If we were to identify that there was a specific risk, then there are a couple ways that we can handle that. One is maybe, through a special control, you could put in a contraindication. I think that Margie said that we normally go with precautions and warnings, but we do have the ability to put in that contraindication.

I think the other thing is that there is a 522 program, which is a postmarket surveillance study, that we can also put into play. So if we feel that there is adequate information but we still -- not adequate information, but if there's information, but we've identified a specific risk, then we can call for a 522 postmarket study to help us gather some additional information.

DR. TALAMINI: Thank you.

Further comments?

DR. SILVERSTEIN: I'm sorry, I know my wife is going to tell me

that I talk too much, but I just have one more comment related to -- we reported that there were no MDRs for these systems. Now, the majority of that, I think, reflects that for drug overdose and poisoning, because the therapies, BioLogic-DT and MARS, generally have been instituted in the last 5 to 10 years. You saw that the last one was approved or cleared for the MARS system back in December of 2012. So I think the paucity of information tells us that the safety for these devices -- and again, I think that reflects for drug overdose and poisoning -- are that they are very, very safe.

So those MDRs don't always reflect what's happening out there in the clinical world because you're not required to report an adverse event to the FDA. But I think that if you compare it to other devices, I think you'll be able to see that the safety profile is excellent for those particular indications. I think, as time goes on, we'll learn more about the safety profile for the MARS and BioLogic-DT, although we already have shown that there are some concerns.

DR. TALAMINI: Dr. Moxey-Mims, you have a question? No.

Dr. Schulman, further questions?

DR. SCHULMAN: Gerry Schulman from Vanderbilt.

If you do a PMA, you're going to be sticking with the hemoperfusion devices used for liver problems. You could get that about the different systems. And say the charcoal hemoperfusion system doesn't work, you know, couldn't the FDA state that?

DR. TALAMINI: Perhaps you could state the question again.

DR. SCHULMAN: Yeah. Well, I mean, you have several different devices. You've got the MARS, you've got the charcoal system, and if you do some more studies on its efficacy and you find out one of those systems isn't working, that could be stated.

DR. TALAMINI: So your question and issue is that if these remain Class III and they all had to go through the PMA process --

DR. SCHULMAN: Right.

DR. TALAMINI: -- they would wind up --

DR. SCHULMAN: Sorting it out.

DR. TALAMINI: -- having that be differentiated.

DR. SCHULMAN: Right.

DR. TALAMINI: Does anybody from the FDA have a comment or clarification on that?

MS. GONZALEZ: Gema Gonzalez from FDA.

So that would be correct. Each manufacturer would have to submit a PMA. We would make an individual determination on that PMA for that device, for the labeling of proposed -- the indications for use that are proposed. And being a PMA, it's a standalone application. It doesn't compare like a 510(k) compares to a predicate device, so it's a standalone determination that we would make on that particular device. And we would look at the labeling, look at the data that was provided, and come to a

determination as to safety and effectiveness. It's a different bar of approval. There's no longer a comparison. It's a determination of safety and effectiveness for that device.

DR. TALAMINI: But further clarification. If they did all go through a PMA, there would be a date set, and if the application wasn't completed by that date, that device would be removed from the market, correct?

MS. GONZALEZ: Correct. So there would be a date set for the submittal of the PMA applications, and the PMAs would be received and then they would be reviewed individually as standalone applications.

DR. TALAMINI: Dr. Fisher, did you have a further comment?

DR. FISHER: No.

DR. TALAMINI: Okay. Dr. Gould.

DR. GOULD: So my general impression is that, for all of these indications, with the possible exception of metabolic derangements, that safety and efficacy and risk/benefit, it's not black and white. It's a little fuzzy, I think, for all of these things. I have the general impression that these devices are used less frequently for drug overdose than they might be for hepatic coma and encephalopathy, but I don't know if that's true or not. I don't know that the number of publications is necessarily the best surrogate for utilization, and I wonder if either the FDA or some of the experts could comment.

First of all, what role does the potential utilization of this device for an indication play in determining whether the risk/benefit equation is favorable for a Class II or a Class III? So if you would see this being utilized heavily for hepatic coma or encephalopathy, would that perhaps push the FDA to recommend that this is a Class III device versus being utilized a lot less frequently for an indication like poisoning? Do we know how many of these devices have been sold, to have any kind of sense on utilization out there?

And then from the experts, perhaps a comment as to what is the standard of care currently for hepatic encephalopathy and comas. Is it something that's being used more and more commonly and will have a bigger role if this is Class II under those indications?

DR. TALAMINI: So, Dr. Gould, clarification. So the heart of your question is, does the FDA weigh the amount of use of the device along with their evaluation, or are they completely independent, whether it's used once or whether it's used one million times in a given year?

DR. GOULD: Exactly.

DR. TALAMINI: Could someone from the FDA clarify?

DR. FISHER: Yeah. Ben Fisher.

So not necessarily. We're going to be looking at, like Gema had said -- you know, for a 510(k), we're doing a comparison against a predicate. For a PMA, it's going to be a standalone.

Boy, there was another question that you had. Oh, I think if we

looked at use, it would -- you know, that would actually give us some more data, I think. If you look at metabolic disturbances here, there's really not the information out there.

When it comes to the number of devices that are actually out there, for 510(k)s it's pretty hard to track. I mean, you could get that information if you looked at companies individually and what they're willing to disclose on how much they have in the way of market share. For a PMA, it's a little bit different because, for a PMA, they're actually required to come in and give us an annual report, and with that annual report, they report to us how many units they've sold. So we do have information on that.

DR. TALAMINI: So your other question, Dr. Gould, was perhaps for one of the clinicians on the Panel, as to how often they're being called to do hemoperfusion for hepatic failure.

DR. GOULD: Yes.

DR. TALAMINI: Is that correct?

DR. GOULD: That's correct.

DR. TALAMINI: Is there somebody on the Panel who's willing to address that?

Dr. Dasarathy.

DR. DASARATHY: Yeah, we probably have the largest or pretty close to the largest transplant center in the nation, and we don't use this. We don't use this with this. We are not convinced that it is the most effective or

beneficial treatment. That doesn't mean that there are not other centers that don't use it. There are people who use it. And I think it also depends on the biases of the individual hepatologist. We have a pretty large group. We discuss these things. MARS has been discussed extensively at our center, whether we should use it, because it looks like most of the experience seems to be European experience. There doesn't seem to be much of its application in terms of transplants in the United States. So I don't know, maybe because we are not convinced that is very helpful.

DR. TALAMINI: Thank you, Dr. Dasarathy.

Dr. Marks.

DR. MARKS: Yeah. Eric Marks.

I'd like to make a comment. One of the other -- in reference to your question. Most of these things have an expiration date, and if you're in a center that doesn't see a lot of poisonings or you're in a center where you get infrequent use, these things are expensive and they expire. And that was our experience at both Walter Reed and Bethesda, that we weren't getting called upon to use them, so we haven't used them in a prolonged period of time. But part of it was the patient load that comes your way, whereas Cherry Hospital emergency room may have more of the use for this, or near a chemical plant.

But the expiration date and the cost also sort of limits the utility if you don't have a big patient population, that you're going to be able

to determine -- it also gets back to the point that I was raising earlier, which is these devices require a certain amount of technical and clinical expertise to use appropriately, as compared to -- and we won't talk about hemodialysis now, but it's not the same thing as doing hemodialysis. There are other constraints. So the aspect of you have an expert on board that knows how to use this under the appropriate circumstances within the time frame that it's been shown to be efficacious -- and the FDA doesn't control that. But at the same time, having them available on the outside leaves that open to their discretion, perhaps. And so it may be a consideration.

DR. TALAMINI: Dr. Afifi.

DR. AFIFI: Abdelmonem Afifi.

If the recommendation that's being -- that we're discussing now is, in fact, implemented by the FDA, then there will be a period of time where some of these devices are available. They're approved for drug overdose and poisoning but not for hepatic coma or metabolic disturbances.

My question is, what stops someone from actually using that device that's available for the purpose of hepatic coma or metabolic disturbance? And what happens if someone actually uses it?

DR. TALAMINI: Would one of our FDA experts like to address that question?

MS. GONZALEZ: We control the labeling, and as you've heard before, we clear the labeling for a specific use and we can put

contraindications, we can put specifications on how it's to be used or who it's to be used by or where it's to be used, if it's a clinic use versus hospital use versus home use. But you're right. Under the practice of medicine, what happens at the clinic stays at the clinic, and it really is based on the individual clinicians. But the labeling is very clear as to what it's indicated for, what it should be used for, and what the limitations are.

DR. TALAMINI: Dr. Schwaitzberg.

DR. SCHWAITZBERG: You know, getting to this issue of Class II, maintaining Class II for the poisoning and overdose, a couple of comments I hear is that its use in futility therapy, that there isn't any good data on efficacy. We keep on getting back to that and we talk about acetaminophen late in the course. We talk about this is the treatment of last resort.

Are there opportunities to address that in the labeling, you know, to say that there is no evidence that there is efficacy in futility therapy or late-stage therapy? Is that wording that can be incorporated, or it's yes or no? I got a yes or no last time; what do I get this time?

DR. SILVERSTEIN: There is a certain amount of information that we can require sponsors to put into their labeling regarding the results of their data. That's the best way I can answer it. We can ask them. If they have done a clinical study, if they have any evidence, we can ask them to provide that in the labeling. And those results then can be used by clinicians to decide whether or not they want to use a device for that specific

indication. It's limited. It's not defined necessarily as for the clearance of this drug, this drug, or this drug.

Certainly, clinicians are expected, along with the labeling, with the renal labeling, to review the literature and to assess whether or not the therapy is the best therapy for the particular indication. But, again, we can't mandate the practice of medicine. We can just hope that people will read the labeling, read the literature, and make a decision based on that.

DR. TALAMINI: So our transcriptionists are going to be angry with us because we haven't been disciplined enough to state our name before speaking into the microphone. This was Talamini.

Go ahead.

DR. NEULAND: This is Carolyn Neuland.

I just wanted to add a couple little things. Number one is that, in the 510(k) world, not everything that goes in the labeling stays in the labeling after we clear it, because we don't control everything in the labeling. I mean, a company can't change the indications for use; they can't change the contraindications. There are other things they just tend to change. If you do a special control in the labeling, then they won't be able to change it. So that's one thing to consider. In PMAs, what we put in the labeling stays in the labeling. So those are just two slightly different ways of looking at labeling. So that might be something you want to talk about.

DR. TALAMINI: That's helpful.

Dr. Fisher.

DR. FISHER: Just a point of clarification because I've heard a couple comments that -- one was to keep things in Class II and to move things to Class III. I just want to be very, very clear. These are all Class III devices right now, so we're not moving anything up and we're not keeping anything in Class II. Our proposal is, right now, that all of these are in Class III. So whatever happens to those Class III devices, if it's a call for a PMA, it's going to go across the board.

DR. TALAMINI: This is Talamini. Thank you, Dr. Fisher.

Dr. Marks, I think, had a further question.

DR. AFIFI: I have a question.

DR. TALAMINI: Okay, Dr. Afifi.

DR. AFIFI: Abdelmonem Afifi again.

As a follow-up to my previous question, if there are no controls on how these devices will be used when there is this mixed classification, is it not cleaner to just simply keep it as a Class III rather than having this mixed classification?

DR. FISHER: Ben Fisher.

I think that's what we're here to ask you guys.

(Laughter.)

MS. SHULMAN: This is Marjorie Shulman.

It does not matter to us. It doesn't matter if it's clean or if it's

all in one or split between the two. I guess that we have many that are split, and it's just we remember the overall goal is to put the device in the lowest class which controls can provide reasonable assurance of safety and effectiveness. So that's the overall goal, to put it in the lowest class that can assure the safety and effectiveness.

DR. FISHER: And Ben Fisher once again for clarification.

I didn't mean to suggest that it was a clean or easy way to do it, just that we're looking for your recommendations as to if they should stay where they are or be moved.

DR. TALAMINI: I think Dr. Woods was next.

DR. WOODS: I have a statement and then a question.

I think, based on some of the discussion here, I do want to make it clear, just as FDA has, we're really discussing safety and efficacy and between Class II and Class III. People are going to use these off label if they choose to, no matter what class they're in, so we shouldn't make a decision on a class based on who we think is going to use it for what indication.

Secondly, for drug toxicity, there are digitalis and phenobarbital -- clearly, those overdoses benefit from hemoperfusion. Acetaminophen -- you know, there are other good therapies out there, and again, we shouldn't be making a decision based on what the alternatives are. We should let these devices stand alone for their safety and efficacy as indicated in the label.

And in terms of the groups of patients looking at liver failure as

opposed to drug toxicity, the FDA has already pointed out, when you see these patients, there's a very clear difference in the people that you're treating. The drug toxicities tend to be people who overdosed either as a suicide attempt or an accidental overdose as in, usually, digoxin, something like that. But these are basically much healthier patients. We know exactly what we're trying to remove from their body. The device is shown to attract that drug and remove it, and it's usually a one-time or two-time therapy and they're done. And they recover or they don't, but it is potentially a life-saving intervention in those situations.

As a gastroenterologist seeing the hepatic failure patients, these patients are very, very sick. We're talking hepatic coma. They are probably going to die, in all likelihood, at some time in the next three to six months. We don't even know what the toxins are potentially that are making them sick. Ammonia is yet one measure, but ammonia levels are not elevated in some hepatic coma patients. There are other things that are un-measurable, and so we don't really know what we're removing from their blood when we are attempting to do hemoperfusion. And I think the data has been pretty sketchy over the years. You know, it's not in wide use because it kind of doesn't work. And the patients who are very sick get transplanted these days. The ones that are non-transplantable, for whatever reason, may be the ones that we might see this device being used in, again, as almost a futile attempt to try to prolong life.

So I have much more concern over the use of that product for the liver failure patients than I do over the indication for the drug toxicities, and I personally feel like dropping the drug toxicity to a II and keeping hepatic failure at a III, is what we should do. And for the hepatic failure, I just think we need more data. I think we need to understand these patients better, understand what their toxins are, and be able to understand better what these perfusion devices are actually removing.

So those are my comments.

I did have one question, and it's a simple one, for the people who do these dialysis procedures: Are we hooking up the patient to a hemodialysis machine but interspersing -- are we just purchasing a carbon thing, you know, that the blood goes through, or is it a whole machine that you have to purchase and that has the hemoperfusion device inside of it?

DR. TALAMINI: So I've been going in order of people asking questions, but if there is a Panel member or an FDA expert that wants to address that question -- yeah, Dr. Schulman.

DR. SCHULMAN: The nephrologists, then, will do all the extracorporeal therapies or anything, red cell exchange for sicklers and so forth. So even though we get referrals from the hepatologists, we used to use the MARS system, and we were responsible for doing the extracorporeal therapy. The machine is separate from the dialysis machine, although you could hook up a continuous renal replacement machine with it. But those

devices are standalone.

DR. TALAMINI: Dr. Schulman, you had a question as well? A further question?

DR. SCHULMAN: No.

DR. TALAMINI: Dr. Rutledge.

DR. RUTLEDGE: Yes, David Rutledge.

Mr. Chairman, I wanted to make a comment regarding Slide 15 about MDR reporting with no MDR reports, and I want to give a sort of slightly different interpretation of that, which I think may be a good opportunity for us to consider as we're addressing these questions a little bit later.

You know, MDRs have a purpose, but they are not hypothesis driven. They're a great way for manufacturers to go into the MAUDE database and look for these reports, to look for why devices are failing, and they're not very good for looking at and calculating rates. And there was a comment made previously that because there's nothing there, these devices are safe. And I would just say that maybe there's a good opportunity for the manufacturers, in general, for us, to include some language for retraining all the employees in the manufacturers, and also maybe site-specific retraining for the sites that are using these devices, more in order to educate them on and increasing the awareness to report MDRs, because from a qualitative standpoint, these MDR reports are very good, but from a quantitative

perspective, they're not.

And the manufacturer wants to know this information; it's good for patients, it's good for the physicians using the devices, and it's good for the family members of these patients. So at some point, as we start addressing the questions, maybe we can have some language around increasing that awareness at the manufacturer and maybe target the training at these sites that are using these products.

DR. TALAMINI: Thank you.

Comment?

DR. FISHER: Yeah, I think you made a very good point, Dr. Rutledge, about the MDR reports. I think the FDA has recognized that there are limitations to MDR reports. We're just receiving what people are sending out. You're not required, if there's an adverse event, to report it, with the device, to the FDA. We certainly encourage that.

The slide that Gema Gonzales put up, in her initial talk, talked about that the lack of reports may be due to under-reporting, which you're talking about. Even when we get MDR reports, at least from my personal experience, I think that we often do not get complete information. We aren't always able to determine if the adverse event, even death, is related to the device or is related to something else, and we try to get more and more information from that.

Some manufacturers receive the reports from patients, but

those aren't always conveyed to the FDA. Patients may not report them. And, again, as you saw, especially for the devices for hepatic coma, there aren't any devices that are being used right now, so it may just simply be -- and Dr. Woods mentioned -- that they may not be used that often, at all, so we're just not getting them because they're not being used that much.

So I think it's a fair point that the number of MDRs doesn't necessarily reflect what the adverse event rate is. However, you can make some general conclusions that if you have no MDR reports over a long period of time where these devices have been used for drug overdose and poisoning, it would, I think, convey the message that the devices have a relatively safe profile.

If I stated that they are safe, I didn't mean to say that and I apologize. I'm just saying that the relative safety profile, compared to other devices where we do see quite a number of MDRs come in, I think, would be inferred from the few or no reports that we've received. But it's a very important point that you make.

Thank you.

DR. TALAMINI: So we're edging towards the specific questions, and I framed this part of the conversation asking about potentially moving all of these devices to Class II. So I want to get any members of the Panel who feel otherwise and want to try and convince the Panel that all of these should remain Class III, to perhaps bring that forward in the very near future as we

edge towards addressing these questions.

Having said that, there are still four folks who have questions out there.

Dr. Faulx.

DR. FAULX: I just have a question.

I agree with, regarding hepatic encephalopathy, that the devices should stay in III. But if we kept the devices for drug overdose in III, does that run the risk that then they have to produce data to show, you know, if they're not used very often and we're talking about a lot of places don't use them anymore, is there a risk that then they'll disappear?

So for patients who, maybe that's their only option, we sort of had something disappear that might -- since we do have more data on those showing that it seems to be safe, does it kind of run the risk that if you keep it in III, that they're going to disappear?

DR. TALAMINI: I see heads shaking from the FDA, but would somebody like to formally address that question?

MS. GONZALEZ: Gema Gonzalez, FDA.

So correct. If everything becomes -- or stays in the Class III, we would need to call for PMAs, and everyone would have to submit a PMA. If a manufacturer chooses not to submit a PMA for a particular device, then that device would have to be pulled off the market. So there's always a risk of not having devices that have traditionally been on the market and used and not

being available anymore.

DR. TALAMINI: And is it your opinion -- this is Talamini -- that that would be difficult for this set of devices given the frequency of use, or can we not make that inference?

MS. GONZALEZ: It's hard to make that inference. Every manufacturer is going to have a business decision to make as to whether they can submit a PMA, whether they can gather data and to answer the questions and show safety and effectiveness for their particular device.

DR. TALAMINI: Dr. Fisher.

DR. FISHER: Ben Fisher.

Yeah, I agree. I mean, the option is for the manufacturer to come forward and to submit the PMA, and if they think that it is in their best business model to move it forward, then they can.

The thing that I want to make clear is that we propose a date for them to come in with a PMA, so the decisions that could be made today aren't going to affect the availability of the device tomorrow. So it will still be available for some time, and if those companies do decide to come in with a PMA, we'll address those submissions accordingly.

DR. TALAMINI: Yes, ma'am.

DR. FOY: Joni Foy, ODE.

Just a further clarification on this issue. The company would have to demonstrate a reasonable assurance of safety and effectiveness

through the PMA process. We certainly also do a benefit/risk assessment. That's part of our assessment with regard to whether or not the device has demonstrated a reasonable assurance of safety and effectiveness, and part of that does take into consideration the patient population for which the device is intended to be used. I just wanted to provide additional clarification with regard to that issue.

There are also additional or different controls that we have with the PMA program in comparison to the 510(k) program -- some of those have been mentioned earlier today -- with regard to annual reports as an additional requirement through the PMA program. Also, manufacturing review coupled with when a company wants to make a modification to the product, there are higher standards, so to speak, with regard to the PMA program; 30-day notices and those kinds of things are necessary to be submitted through the PMA program, which are not a requirement through the 510(k) program.

DR. TALAMINI: Dr. Simon.

DR. SIMON: I found Dr. Woods' comments very helpful, and so it just seems like the change in the status quo here is to actually move the poisonings into Class II. Otherwise, if we just do nothing, everything stays Class III, as it is.

So what would be helpful for -- and I don't treat poisoning. I have placed the catheters in cases where a patient is going to go on to

hemoperfusion. But for those in the room that treat poisonings -- and the reason I found her comments helpful was just to hear like, yes, hemoperfusion has a role in poisoning; it is safe, it's effective.

But just to hear, for those who do, maybe for those of us who don't, maybe a little more understanding of exactly what this role is, because I think that is helpful -- at least, it was for me -- in informing my decision, which I'm pretty, at this point, understanding in the sense of it makes sense to move this one group into Class II, but to certainly hear, if anyone else treats poisoning, to know where this fits into standard of care on poisoning.

DR. TALAMINI: One of our nephrologists on the Panel willing to address that briefly?

Dr. Schulman.

DR. SCHULMAN: Gerald Schulman from Vanderbilt.

There are certain drugs that are better removed with hemoperfusion. And, again, to those drugs that are highly protein-bound, it's a good therapy, and I think it should be included in our armamentarium to treat these patients.

DR. SIMON: I should say it's safe, as well, if I can quote Dr. Silverstein.

DR. SCHULMAN: Yes.

DR. SIMON: Do you agree?

DR. SCHULMAN: Yes.

DR. SIMON: Okay.

DR. TALAMINI: Well, we have to be a little bit careful because we can hear from our clinicians, but it's the data that really needs to drive the decisions.

This is Talamini as the Chair.

So it's helpful contextually, but we do have to be careful.

Dr. Agodoa.

DR. AGODOA: I'm still hung up on the safety issue. The devices are not being used as much anymore, and so what we have here, in publication, is old data from the '70s. We are not getting very much anymore, and the MDRs are not telling us anything about these, so why can't we get more information, have everybody submit the information through the PMAs? At this point, then, we can evaluate, maybe, in another 5-10 years we would be in a better position to get more recent data and make that decision at that point, whether we should move them to Class II or not. I'm not sure about the usage at this point.

DR. TALAMINI: So hold that opinion because you'll be able to offer it as we go around the room for the specific questions. I want to make sure we get to other folks that are on the list with questions.

Dr. Coldwell.

DR. COLDWELL: I think I've been asked and answered.

Thank you.

DR. TALAMINI: Okay.

Dr. Afifi, further question?

DR. AFIFI: No, not at this time.

DR. TALAMINI: Dr. Moxey-Mims.

DR. MOXEY-MIMS: So my question is a follow-on to what Dr. Agodoa was saying, and I don't know if FDA has the answer to this.

Is it that there's less in the literature because, in fact, there is more use and it's become more standard, so people just aren't publishing about it anymore, or is it that there's less use? And maybe you can't answer that, but I'm wondering if it may be the contrary of what you're thinking and not that it's not in use but it's become so routine that nobody's publishing it anymore.

DR. TALAMINI: Dr. Schwaitzberg.

DR. SCHWAITZBERG: Quick technical question.

Most of us who have sat on these panels were responding to clinical trial data, and in this determination, we're looking at old studies and old data, and it's a little out of our comfort zone for what we have usually come here for. I just want to make sure I'm not making a fundamental mistake.

Does PMA equal new clinical trial?

And I think I got a little sense of worry that if you put the manufacturers through a new clinical trial for a therapy that many people are

going -- is standard and acceptable and it works, it makes us uncomfortable that we're putting an unreasonable burden in certain categories of diseases.

So can somebody submit a PMA and get the benefits of all these labeling controls and all this without going through a new clinical trial?

DR. NEULAND: They would submit whatever data they have on their device. So they put forth an argument that what they have, whether it's trial design, studies they've done, or other data they've collected, they put that forth and we will review it. And we'll probably bring it to an advisory panel like you to -- so basically, that's it. And if we find it's not sufficient, they will have to go do another trial.

So it really depends on whether they can demonstrate reasonable assurance of safety and effectiveness with the information they have, as a standalone device, not as substantially equivalent to something that might have been not a very good device in the past.

DR. TALAMINI: Dr. Fisher.

DR. FISHER: And just to add to that, when we bring this to panel and if there are some decisions, one of the options that we do have that we can exercise is to collect postmarket data on that also.

DR. TALAMINI: So we need to move to the specific questions, but I would ask the Panel, this is the last opportunity for Panel members to directly address questions to the FDA. If a Panel member has a burning remaining question to address to one of our FDA experts, now is the moment.

Dr. Faulx.

DR. FAULX: Can I just ask maybe a dumb question, but premarket versus postmarket is confusing because they're already on the market, so I kind of thought that PMA, even though it's premarket, is really after that it's already out there, gives us data. Is that right or wrong?

MS. GONZALEZ: Gema Gonzalez, FDA.

I think Dr. Fisher was referring to postmarket in the case if there is a PMA and there may or may not be sufficient information. If there is enough information to substantiate safety and effectiveness, they can get approval, but sometimes a panel might recommend "we'd like to have long-term data, I would like to have more extensive data," and so they'll do a postmarket study, and that's very common for PMA devices.

So, yeah, it's a confusing aspect because these devices are on the market, and so essentially anything that happens now is postmarket. But there is no requirement to collect the information; so under clinical use, they're using the devices, they're not collecting data. But with a PMA, there might be a postmarket condition that they'll have to collect data under a protocol.

DR. MARKS: I have a specific question.

Eric Marks.

There's an international consortium that's being developed to look at hemoperfusion across a lot of countries, and actually they're in

preparation of determining what kinds of questions -- so in relationship to what we're talking about now, decisions that are made now would then be subject if new data came into the literature about these devices and the FDA became aware of that, then there would be the opportunity, I suspect, to reevaluate a decision that was made at this particular period of time in light of international data that would meet some of the criteria here.

So I want clarification. It wouldn't necessarily be collected by the manufacturers as part of the post- or premarketing issue; it would be something that would be coming from an international consortium -- and I'm sorry, I can't remember the acronym at the moment, but I can provide it to you -- that's looking at this. So there would be a chance to re-review this at some point in the future based upon new literature?

DR. FISHER: Ben Fisher, FDA.

So if I understand your question, if we were to move some of these to Class II, would there be an opportunity at some other date to possibly reevaluate these and put these back up to Class III?

DR. MARKS: Yes, if data became available that wasn't present now in terms of a lot of the questions that have been raised. There is standard of care, utility, specific use, risk/benefit ratio. So if that then became available, would then the FDA be able to go back and look and say well, based upon what we know now, based upon -- better than 1990, this is the decision at this moment?

DR. FISHER: So the answer is yes, we could up-classify a class of devices.

DR. MARKS: Okay, thank you.

DR. TALAMINI: This is Talamini as the Chair.

So we're now going to move to the specific questions.

And I want to remind the Panel that, different from other panels, we are not voting. This is not looking for a vote that goes in one direction or another. This Panel may have a consensus regarding these questions, which would be terrific; it may not have a consensus.

And I believe what the FDA is most interested in is hearing the opinions of the experts that are around the table. So this is a little different in that we're not driving towards a vote that goes in one direction or another. What we are interested in are the opinions of the experts and whether a consensus does emerge based on our conversations this morning.

So having said that, at this point, let us focus our discussion on the FDA questions. Copies of the questions are in your folders. I want to remind the Panel that this is a deliberation period among the Panel members only. Our task at hand is to answer the FDA questions based on the data in the panel packs, the presentations we heard this morning, and the expertise around the table.

With this said, I would ask that each Panel member identify him or herself each time he or she speaks to facilitate transcription.

Please show the first question.

And, again, a privilege of the Chair, there are a fair number of questions here with subparts. We may try and coalesce the subparts of each question into one unit and go around the table with that individual question in the interest of time, because we do have a separate topic to take up this afternoon.

So if we could have the first question, please.

MS. GONZALEZ: Thank you.

Question Number 1: FDA has identified the following risks to health for hemoperfusion devices for various indications based on the input of the original classification panel, review of industry responses to the 2009 515(i) order, the 2012 proposed rule, and the 2013 proposed order, and FDA's literature review:

- Extracorporeal leaks (blood loss);
- Platelet loss and thrombocytopenia;
- Leukopenia;
- Hemolysis;
- Leak of adsorbent agent into fluid path (release of emboli);
- Lack of sterility;
- Toxic and/or pyrogenic reactions;
- Infection;
- Hypotension;

- Lack of biocompatibility in materials or solutions contacting blood;
- Clotting (blood loss);
- Removal or depletion of vital nutrients, hormones, vitamins, substances and drugs (e.g., adsorption of glucose, unspecific removal characteristics, drop in patients' hematocrit), due to device's lack of specificity;
- Metabolic disturbances;
- Lack of effectiveness – failure to remove drugs in drug overdose, or bring on clinical improvement in hepatic encephalopathy/failure, inadequate adsorption;
- Treatment interruptions or discontinuations;
- Electrical shock due to lack of electrical safety;
- Electromagnetic interference, which may lead to adverse interactions with other patient systems.

a) Please comment on whether this is a complete and accurate list of the risks to health presented by sorbent hemoperfusion devices.

b) Please comment on whether you disagree with inclusion of any of these risks, or whether you believe any other risks should be included in the overall risk assessment of sorbent hemoperfusion devices, specifically for the treatment of

drug overdose, poisoning.

c) Please comment on whether you disagree with inclusion of any of these risks, or whether you believe any other risks should be included in the overall risk assessment of sorbent hemoperfusion devices, specifically for the treatment of hepatic coma or metabolic disturbances.

DR. TALAMINI: Thank you.

So we'll go around the table clockwise for this first question. And, again, I think we can do (a), (b), and (c) together with respect to this list.

Dr. Marks.

DR. MARKS: I actually have no additional comments to add to this. I think the list is comprehensive, and I agree with the inclusion of the materials that are there. So I don't have anything to add. I think it's a comprehensive list.

DR. TALAMINI: Thanks, Dr. Marks.

Dr. Afifi.

DR. AFIFI: I also have nothing to add.

DR. TALAMINI: Thank you.

Dr. Schulman.

DR. SCHULMAN: Gerald Schulman.

I think that the difference between the use of these devices for drug poisoning versus the hepatic problems -- and so as the speaker

mentioned before, for poisonings, it's probably one treatment, and so the risk of losing nutrients and things like the good stuff in blood is probably low with respect to the poisoning.

DR. TALAMINI: So this list is okay with you, nothing to add, nothing to take away?

DR. SCHULMAN: Yes.

DR. TALAMINI: Thanks, Dr. Schulman.

Dr. Dasarathy.

DR. SCHULMAN: I just would probably stress, for the poisonings, you know, things like nutrient depletion and so forth are minimal.

DR. TALAMINI: Thanks.

Dr. Dasarathy.

DR. DASARATHY: Nothing to add.

This is Dasarathy from Cleveland Clinic.

Nothing to add.

DR. TALAMINI: Thank you.

Dr. Agodoa.

DR. AGODOA: Larry Agodoa, NIH.

I have nothing else to add.

DR. TALAMINI: Thank you, Dr. Agodoa.

Dr. Sjogren.

DR. SJOGREN: Sjogren.

I have nothing to add. I'm in agreement.

DR. TALAMINI: Thank you, Dr. Sjogren.

Dr. Faulx.

DR. FAULX: I have nothing to add, thanks.

DR. TALAMINI: Dr. Simon.

DR. SIMON: The only good thing, actually, with that is the systems don't get used without placement of a catheter, so actually put on the list as well, catheter risks.

DR. TALAMINI: Actually, this is telling me -- the Chair.

Can we put back up the list? That's probably more helpful to us than -- we can't get it one slide, but perhaps leave that slide up, as we deliberate this.

Thank you, Dr. Simon.

Dr. Woods.

DR. WOODS: I have nothing to add. I think the list is comprehensive.

DR. TALAMINI: Thank you.

Dr. Gould.

DR. GOULD: Jon Gould.

I have nothing to add.

DR. TALAMINI: Dr. Moxey-Mims.

DR. MOXEY-MIMS: Marva Moxey-Mims, NIH.

I have nothing to add.

DR. TALAMINI: Dr. Coldwell.

DR. COLDWELL: Coldwell.

I have nothing to add.

DR. TALAMINI: Dr. Pavlovich.

DR. PAVLOVICH: Pavlovich.

Nothing to add.

DR. TALAMINI: Dr. Schwaitzberg.

DR. SCHWAITZBERG: I have nothing to add, but I wouldn't put the catheter risks in. I think that's its own device and it would just -- the risks are for this device. The catheter risks are their own category.

DR. TALAMINI: Thank you, Dr. Schwaitzberg.

Ms. Chauhan.

MS. CHAUHAN: Cynthia Chauhan.

Nothing to add.

DR. TALAMINI: Thank you.

Dr. Rutledge.

DR. RUTLEDGE: David Rutledge.

Nothing to add.

DR. TALAMINI: Thank you.

And Dr. Fennal.

DR. FENNAL: Mildred Fennal.

Nothing to add, thank you.

DR. TALAMINI: Thank you.

So, Dr. Fisher, with respect to Question 1, really parts (a), (b), and (c), it sounds like the consensus of the Panel is that the list is complete.

Is that sufficient?

DR. FISHER: Thank you very much, yes.

DR. TALAMINI: All right. Second question.

MS. GONZALEZ: Question 2: According to 21 C.F.R. 860.7(d)(1), "there is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. The valid scientific evidence used to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of illness or injury association with the use of the device for its intended uses and conditions of use."

In addition, according to 21 C.F.R. 860.7(e)(1), "there is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results."

FDA believes that the available scientific evidence supports a reasonable assurance of safety and effectiveness of sorbent hemoperfusion systems when used for the treatment of drug overdose or poisoning.

a) Please discuss whether you believe the available scientific evidence is adequate to demonstrate the safety and effectiveness of sorbent hemoperfusion systems for these indications for use.

b) Please comment on whether the probable benefits to health from use of sorbent hemoperfusion systems for these indications for use outweigh the probable risks to health.

DR. TALAMINI: Thank you.

So we've already had -- this is Talamini, the Chair.

We've already had a fair airing out of this issue, which is good. So now what we need from each Panel member is your opinion in this regard regarding risks and benefits.

So we'll begin going the other direction with Dr. Fennal.

DR. FENNAL: Mildred Fennal.

I agree that the scientific data that is available is adequate to demonstrate the safety and effectiveness of the hemoperfusion system. And I do believe that the benefits for health outweigh the risks.

DR. TALAMINI: Thank you, Dr. Fennal.

Dr. Rutledge.

DR. RUTLEDGE: Yes, David Rutledge.

I'm going to concur and just say that because -- I am swayed here, and I'd like to see more data, but why I'm swayed to agree with this is because of the acute nature and the use of the device in this acute setting of drug overdose or poisoning. I think that the data is adequate for this particular indication.

DR. TALAMINI: Thank you.

Ms. Chauhan.

MS. CHAUHAN: I agree that in drug overdose or poisoning, as you said, the acute use is a good use, and so I support that.

DR. TALAMINI: Thank you.

Dr. Schwaitzberg.

DR. SCHWAITZBERG: Steve Schwaitzberg.

I have nothing to add. I agree.

DR. TALAMINI: Thank you.

Dr. Pavlovich.

DR. PAVLOVICH: I substantially agree. However, I would like to comment that it seems as though these systems are not being used very often, and it sounds as though they're safe and effective, particularly in trained hands and experienced hands. And yet, I think they carry a lot of risk because they're sitting on a shelf in the back of a dialysis clinic and every 10

years they're used.

Secondly, any discussion of benefits versus risks, at least in the surgical literature, which I'm more familiar with, the elective surgical literature involves informed consent, and here we have completely at-risk, highly at-risk population that can't consent. And that may completely be not relevant here, but I think if there was a machine that would save eight out of ten patients who had overdosed on something, but once in a while it would kill one of those patients or dehydrate them or something, in most settings, one could sort of weigh that and the patient would be involved with the decision.

Here that is not the case. Most of these patients probably cannot give consent given the state that they come in with, and that's even more the case in the coma setting, which we'll discuss later. So that did not come up at all. We mentioned at-risk population, and then it just sort of fell off, and I just think it's difficult to -- my sense would be that yes, the benefits outweigh risks when these systems are used in trained hands, but that it's going to be hard, in individual cases, to make a decision. And since the patient is not involved with it, we have to add a little bit more scrutiny, and if that means Class III versus Class II, fine. I don't think that means that, and I think I'd rather, overall, have these available as a Class II, but I just had to sort of put that out there.

DR. TALAMINI: So with those comments, in general, you agree

that the benefits outweigh the risks based on the data?

DR. PAVLOVICH: Yeah. And more importantly, I wouldn't want to put undue burden on new drug overdose or poisoning systems that might come out to have to show lots of data and thereby not be able to come out because of that. But if anyone else has thoughts about that, these at-risk situations, I'd be happy to hear them.

DR. TALAMINI: Thank you.

Dr. Coldwell.

DR. COLDWELL: Coldwell.

I'm a little uncomfortable with the lack of data that's available. However, I do believe that, given the paucity of data, it still is enough to sway me to believe that it is safe and effective, and the benefits outweigh the risks.

DR. TALAMINI: Thank you, Dr. Coldwell.

Dr. Moxey-Mims.

DR. MOXEY-MIMS: Marva Moxey-Mims, NIH.

I also agree with (a) and (b) for Question 2. And just to follow up on your issue of consent, at least from the standpoint of pediatric patients, the parent would consent whether it's this or even hemodialysis. Somebody has to consent. I can't speak for the adult world and what they would do there.

DR. TALAMINI: Thank you.

Dr. Gould.

DR. GOULD: Jon Gould.

I think that the data is adequate, and that's probably the best word, to demonstrate safety and effectiveness. And I also believe that the probable benefits outweigh the risks.

DR. TALAMINI: Thank you.

Dr. Woods.

DR. WOODS: Karen Woods.

I agree as well that (a) and (b) -- I can support those.

DR. TALAMINI: Okay, thank you.

Dr. Simon.

DR. SIMON: I back the decision of the FDA on (a) and (b).

DR. TALAMINI: Thank you.

Dr. Faulx.

DR. FAULX: I agree as well with (a) and (b).

DR. TALAMINI: Dr. Sjogren.

DR. SJOGREN: I agree with both.

DR. TALAMINI: Thank you.

Dr. Agodoa.

DR. AGODOA: Larry Agodoa, NIH.

I am concerned that we have too much old data to base our decisions on. I think we need new scientific evidence that these are still safe, and having the stuff in Class III doesn't mean that they're not going to be

available for use. It still will be there when we need them. So I think we need more data.

DR. TALAMINI: So you're unsatisfied with the data? Which is fine obviously. I just want to be clear.

DR. AGODOA: Yeah, they are too old. What we have from the literature is too old for my comfort.

DR. TALAMINI: Okay, thank you.

Dr. Dasarathy.

DR. DASARATHY: I agree with the recommendations.

This is Dasarathy from the Cleveland Clinic.

DR. TALAMINI: Thank you.

Dr. Schulman.

DR. SCHULMAN: Gerald Schulman.

I agree with the (a) and (b).

DR. TALAMINI: Thank you, Dr. Schulman.

Dr. Afifi.

DR. AFIFI: Abdelmonem Afifi.

From an epidemiologic and statistical point of view, I agree with the FDA's conclusion.

DR. TALAMINI: Thank you.

Dr. Marks.

DR. MARKS: I have a caveat to the comment I'm going to make.

I am troubled, as stated by Dr. Agodoa, with the comment here, when used for the treatment of drug overdose or poisoning.

I think that the data that we do have that's valid are about specific drug classifications, and without some type of awareness on the fact that this does not have utility across the spectrum for drugs, the way this is currently written, I couldn't accept this unless the caveat was that we're talking about very specific issues that would -- very specifically carried out in the special controls -- that, you know, essentially this is prohibited for use for drugs for which there is no benefit. That would go along with the effective medicine.

So I'm willing to accept the recommendations but the caveat, when we talk about special controls, is that we have to be very specific about those agents for which these materials are going to be used.

DR. TALAMINI: Thank you, Dr. Marks.

So, Dr. Fisher, with respect to Question 2, the Panel generally agrees with the data supporting safety and efficacy for drug overdose and poisoning with one clear, strong negative voice and one set of provisos.

Is this adequate?

DR. FISHER: Thank you very much, yes.

DR. TALAMINI: All right, Question 3.

MS. GONZALEZ: Question 3: FDA believes that the following Special Controls can adequately mitigate the risks to health for sorbent

hemoperfusion devices when used for the treatment of drug overdose or poisoning, and can provide sufficient evidence of safety and effectiveness:

Proposed Special Controls

- The device should be demonstrated to be biocompatible;
- Performance data to demonstrate the mechanical integrity of the device (e.g., tensile, flexural, and structural strength), including testing for the possibility of leaks, ruptures, release of particles and/or disconnections;
- Performance data to demonstrate device sterility and shelf life;
- Bench performance data to demonstrate device functionality in terms of substances, toxins, and drugs removed by the device, and the extent that these are removed when the device is used according to its labeling;
- Summary of clinical experience with the device that discusses and analyzes device safety and performance, including a list of adverse events observed during the testing;
- Labeling controls, including appropriate warnings, precautions, cautions, and contraindications statements to alert and inform users of proper device use and potential clinical adverse effects, including blood loss, platelet loss,

leukopenia, hemolysis, hypotension, clotting, metabolic disturbances, and loss of vital nutrients and substances. Labeling recommendations must be consistent with the performance data obtained for the device, and must include a list of the drugs the device has been demonstrated to remove, and the extent of removal/depletion; and

- For those devices that incorporate electrical components, appropriate analysis and testing to validate electrical safety and electromagnetic compatibility.

a) Please discuss whether you agree that the proposed special controls are adequate to mitigate the risks to health for hemoperfusion devices when used for the treatment of drug overdose and poisonings, and to provide reasonable assurance of safety and effectiveness.

b) Please comment on whether you disagree with inclusion of any of these special controls, or whether you believe any other special controls are necessary.

DR. TALAMINI: Thank you.

So we'll go the other direction, just go around.

Dr. Marks, the special controls.

DR. MARKS: All right. Redundancy for a point.

The special controls have to, in my mind, address the issue that

I brought forward earlier about the specificity of the use of these devices. I would also suggest that, if we're looking at Bullet Points 3 and 4, we're talking about bench performance. I also believe that it would be important to collect clinical performance data on these, information, because the bottom line is that you can clear something, but the clinical aspects and the outcome that you're trying to obtain is not necessarily the same, and since, from the safety standpoint and efficacy standpoint, it's really patient outcome and not whether or not you have a 25% initial clearance on the bench.

So I would suggest that for the special controls, that we also ask for a summary of clinical experiences, not just looking at adverse events, but at the outcome around the specific poisons and drugs that we include in our recommendations for the use of these devices.

With those two thoughts in mind, I'm willing to accept the recommendations of the special controls with that addition, as mentioned.

DR. TALAMINI: Thank you, Dr. Marks.

Dr. Afifi.

DR. AFIFI: Abdelmonem Afifi.

In reading the material ahead of the meeting, I had some questions about the special controls, but they were, I think, clarified during this meeting. Thank you to everyone. And I do agree that they should be included, and I agree with both (a) and (b).

DR. TALAMINI: Thank you.

Dr. Schulman.

DR. SCHULMAN: Gerald Schulman.

I agree with the bullet points, but I also support what Dr. Marks said about some clinical information as well.

DR. TALAMINI: So Dr. Schulman, Dr. Marks put forth two, sort of, additional points, one about the specificity of the drugs and the second about collecting clinical data. You were referring to both?

DR. SCHULMAN: Oh. Both of them, yes.

DR. TALAMINI: Thank you.

Dr. Dasarathy.

DR. DASARATHY: I agree with all of them and all remarks, but I had a question. I'm not sure having more bench studies is so important. I think it's much more relevant to do clinical data collection than adding more bench studies to this. This is just asking for more, which is not going to be applied for us. But, otherwise, I agree with what the recommendations are.

DR. TALAMINI: So is it your suggestion that some of the bench studies be removed from the special controls list?

DR. DASARATHY: That is correct. Bench studies are not giving us much information. This is just adding more burden to the manufacturers, and I think one of the FDA people did say that if you put too much burden, it's not going to be a scientific or a clinical decision, it's going to be a business decision and things will go just go off. They will not be available. So we

might end up pushing for more and more, which is not going to be applicable, and in the end lose the whole product. So this is something that we really need to be cognizant of.

DR. TALAMINI: I think I understand. Thank you, Dr. Dasarathy.

Dr. Agodoa.

DR. AGODOA: Larry Agodoa, NIH.

I agree with all of the special controls, and in addition, I agree with Dr. Marks about the patient safety data and specific drugs.

DR. TALAMINI: Thank you, Dr. Agodoa.

Dr. Sjogren.

DR. SJOGREN: Maria Sjogren.

I agree with Dr. Marks in putting more clinical data into the safety controls. Other than that, I agree with (a) and (b).

And I disagree with removing the bench controls. I think we don't have enough evidence to say that at this point, so I'd like to keep it intact.

DR. TALAMINI: Thank you.

Dr. Faulx.

DR. FAULX: I agree with the special controls. I don't really have anything to add.

DR. TALAMINI: Thank you.

Dr. Simon.

DR. SIMON: I agree with the (a) sub-point. I believe the controls are adequate, and I have nothing to add on the (b) sub-point.

DR. TALAMINI: Thank you.

Dr. Woods.

DR. WOODS: Karen Woods.

I agree with the special controls. I also agree with Dr. Marks' suggestion regarding the specific toxins and the clinical data. And I also do believe that bench performance data should continue for any new drugs that come forth. I'd like to know, at least in the lab, that they actually stick to the hemoperfusion device before we go into clinical trials.

DR. TALAMINI: Thank you.

Dr. Gould.

DR. GOULD: Jon Gould.

I agree with what Dr. Woods actually just said. I believe that additional clinical data would be useful, and some bench top data will help guide the clinical experience in my opinion.

DR. TALAMINI: Thank you, Dr. Gould.

Dr. Moxey-Mims.

DR. MOXEY-MIMS: Marva Moxey-Mims, NIH.

I agree with the special controls outlined in the document and would also agree with Dr. Marks' additions.

DR. TALAMINI: Thank you.

Dr. Coldwell.

DR. COLDWELL: Coldwell.

I agree with both points and agree with Dr. Marks' two points and also believe that the bench testing is of value.

DR. TALAMINI: Thank you.

Dr. Pavlovich.

DR. PAVLOVICH: I agree with point (a) and have nothing to add regarding point (b).

DR. TALAMINI: Thank you.

Dr. Schwaitzberg.

DR. SCHWAITZBERG: Steve Schwaitzberg, Cambridge.

I agree that the strength of the recommendation is beefing up the special controls. I think the point has been made that the safety data has been pretty old and this is the opportunity to update it. There is not an overwhelming amount of literature that the manufacturers couldn't summarize what's known and what's not known and what's known to be ineffective and would support that.

And nothing to add on point (b).

DR. TALAMINI: Thank you, Dr. Schwaitzberg.

Ms. Chauhan.

MS. CHAUHAN: Cynthia Chauhan, Patient Representative.

I agree with both points, and I support Dr. Marks' points that he

made.

DR. TALAMINI: Thank you, Dr. Chauhan.

Dr. Rutledge.

DR. RUTLEDGE: David Rutledge.

I want to say I agree with the bullet points that are listed here. I want to expand on Bullet Point 4 to reiterate about an opportunity that may exist between the Agency and the manufacturers to engage in a discussion for MDR retraining with the manufacturers, and also requesting the manufacturers to do some targeted training at the sites where these devices are predominantly being used as far as increasing the sensitivity for MDR reporting.

And, number two, I would think that this may be a good example of maybe how the industry can get together with a professional society and actually generate a registry for patients using devices like this and all the manufacturers would contribute.

It would do a couple things. One, it would provide clinicians and this Panel, in the future, with independent confirmation about the performance of the device, especially if run by a professional society, as an example. And also it would be least burdensome for each of the manufacturers as they partner and work together under the umbrella of some organization in order to make this happen, moving forward.

So I would just say for the Agency to consider having discussion

with the manufacturers to partner with a society to be able to collect some data moving forward.

DR. TALAMINI: Thank you, Dr. Rutledge.

Dr. Fennal.

DR. FENNAL: Mildred Fennal.

I agree with all the points that have been made, but I wonder if the FDA -- this instrument is so old and it's been around for so long, could we ask the company for their quality control on this particular instrument? That might support some of the points that you've made or not.

DR. TALAMINI: Yeah, at this stage we can't directly ask the FDA questions, so --

DR. FENNAL: Oh. I'm so sorry.

DR. TALAMINI: No, that's fine. But in general --

DR. FENNAL: In general, I'll agree --

DR. TALAMINI: Okay.

DR. FENNAL: -- with all of the points that have been made around the table.

DR. TALAMINI: Okay, terrific. Thank you.

So, Dr. Fisher, with regard to Question 3, the Panel generally agrees with the special controls with a fairly strong consensus for adding specificity with regard to specific elements to be removed by this therapy and to collect further clinical data. I think you also heard the comments regarding

bench controls and targeted training.

Is that adequate?

DR. FISHER: Yes. I'd like to thank Dr. Marks, Dr. Schwaitzberg, Dr. Rutledge, for your comments.

Dr. Fennal, I heard your comment also. Thank you very much.

And I appreciate the Panel's discussion on the bench testing, so thank you.

DR. TALAMINI: Question 4.

MS. GONZALEZ: Question 4: FDA believes that the safety and effectiveness of sorbent hemoperfusion devices when used in the treatment of hepatic coma or metabolic disturbances is not well established. This is based on the lack of valid, scientific evidence in those uses, including the limited number of devices cleared by FDA for those uses, the inconclusive evidence from the published scientific literature regarding the benefit/risk ratio of these devices when used for those indications, and on the general risk we believe they pose to their target patient population.

a) Please comment on whether you agree that the available valid scientific evidence is not adequate to support the safety and effectiveness of sorbent hemoperfusion devices when used in the treatment of hepatic coma or metabolic disturbances.

b) If you do not agree, please explain by identifying and

discussing the following:

i) the valid scientific evidence available in support of a reasonable assurance of safety and effectiveness of sorbent hemoperfusion systems when used in the treatment of hepatic coma or metabolic disturbances; and

ii) special controls that you believe would be sufficient to mitigate the risks to health and provide a reasonable assurance of safety and effectiveness of sorbent hemoperfusion systems when used in the treatment of hepatic coma or metabolic disturbances.

DR. TALAMINI: Thank you.

So we'll go the other direction.

Dr. Fennal.

DR. FENNAL: Mildred Fennal.

I agree that the available valid scientific evidence is not adequate to support the safety and effectiveness of this device when used in the treatment of hepatic coma or metabolic disturbances, one of the reasons being that I have some difficulty with looking at treatment of metabolic disturbances, hepatic coma, and the definition by the FDA of what is life-sustaining and life-supporting.

DR. TALAMINI: Thank you, Dr. Fennal.

Dr. Rutledge.

DR. RUTLEDGE: Yes, David Rutledge.

Mr. Chairman, yes, I do agree that there is lack of valid scientific evidence to support the safety and efficacy of these systems for the treatment of hepatic coma and metabolic disturbances.

DR. TALAMINI: Thank you.

Ms. Chauhan.

MS. CHAUHAN: Cynthia Chauhan, Patient Representative.

I agree and have nothing to add to what Dr. Rutledge said.

DR. TALAMINI: Thank you.

Dr. Schwaitzberg.

DR. SCHWAITZBERG: Steve Schwaitzberg from Cambridge.

I agree there is insufficient evidence to talk about the effectiveness, but I don't know that the safety profile is dramatically different than what is used for other indications in view of the fact that these patients are much sicker. They have a whole bunch of reasons to have low platelets, such as splenic sequestration and things like that. So if you have to take it as a package of safety and effectiveness, I would agree that the data is lacking.

DR. TALAMINI: Thank you.

Dr. Pavlovich.

DR. PAVLOVICH: I also agree that the data are lacking, so I agree with point (a).

DR. TALAMINI: Okay. Thank you, Dr. Pavlovich.

Dr. Coldwell.

DR. COLDWELL: Coldwell.

I agree with (a).

DR. TALAMINI: Thank you.

Dr. Moxey-Mims.

DR. MOXEY-MIMS: Marva Moxey-Mims, NIH.

I agree with (a).

DR. TALAMINI: Thank you.

Dr. Gould.

DR. GOULD: Jon Gould.

I agree with (a).

DR. TALAMINI: Thank you.

Dr. Woods.

DR. WOODS: Karen Woods.

I agree with (a).

DR. TALAMINI: Dr. Simon.

DR. SIMON: Dan Simon.

I agree with (a).

DR. TALAMINI: Dr. Faulx.

DR. FAULX: Ashley Faulx.

I agree with (a) as well.

DR. TALAMINI: Dr. Sjogren.

DR. SJOGREN: Maria Sjogren.

I totally agree with (a).

DR. TALAMINI: Thank you.

Dr. Agodoa.

DR. AGODOA: Larry Agodoa, NIH.

I agree there's not enough current evidence, scientific evidence.

DR. TALAMINI: Thank you.

Dr. Dasarathy.

DR. DASARATHY: Dasarathy, Cleveland Clinic.

I agree with (a).

DR. TALAMINI: Thank you.

Dr. Schulman.

DR. SCHULMAN: Gerald Schulman.

I agree with (a).

DR. TALAMINI: Thank you.

Dr. Afifi.

DR. AFIFI: Afifi.

I agree with 4(a).

DR. TALAMINI: Thank you.

Dr. Marks.

DR. MARKS: Eric Marks.

I agree with (a).

DR. TALAMINI: So, Dr. Fisher, with respect to Question 4, we have unanimous opinion that they agree with 4(a).

DR. FISHER: Thank you very much.

DR. TALAMINI: Question 5.

MS. GONZALEZ: Question 5: Section 513 of the Food, Drug, and Cosmetic Act states a device should be Class III if:

I. Insufficient information exists to determine that general controls are sufficient to provide reasonable assurance of its safety and effectiveness or that application of special controls would provide such assurance, and

II. If, in addition, the device is life-supporting or life-sustaining, or for a use which is of substantial importance in preventing impairment of human health, or if the device presents a potential unreasonable risk of illness or injury.

Regarding Requirement I above, please discuss the following:

a) Whether you believe that the application of general controls, required for all medical devices, are insufficient to provide a reasonable assurance of safety and effectiveness for sorbent hemoperfusion systems.

b) Whether you agree or disagree with FDA's view that the

application of general controls, and the special controls proposed in Question 3 above, are sufficient to provide reasonable assurance of safety and effectiveness for sorbent hemoperfusion systems when intended for use in the treatment of drug overdose or poisoning.

c) Whether you agree or disagree with FDA's view (in Question 4) that there is insufficient information to determine whether special controls can be established to provide a reasonable assurance of safety and effectiveness of sorbent hemoperfusion systems when intended for the treatment of hepatic coma or metabolic disturbances.

Regarding Requirement II above, please discuss the following:

d) Whether you believe that sorbent hemoperfusion systems when intended for use in the treatment of drug overdose or poisoning are life-supporting or life-sustaining, or for a use which is of substantial importance in preventing impairment of human health, or present a potential unreasonable risk of illness or injury.

e) Whether you believe sorbent hemoperfusion systems when intended for the treatment of hepatic coma or metabolic disturbances are life-supporting or life-sustaining, or for a use which is of substantial importance in preventing

impairment of human health, or present a potential unreasonable risk of illness or injury.

Please note that the question above refers to Class III eligibility only; the next questions will ask for a final recommendation for device classification.

DR. TALAMINI: So this is a tough one.

(Laughter.)

DR. TALAMINI: Dr. Marks.

DR. MARKS: I think that, to maintain my own sanity, I'm going to go through this.

I agree with (a), that general controls are insufficient to provide the appropriate assurance.

And I agree that the application of general controls and the special controls that we've already discussed are sufficient to deal with the safety and effectiveness of these systems with regard to drug overdose or poisoning.

I also agree -- and this is now (c) -- that there is insufficient data to determine whether or not special controls can be established for hemoperfusion systems with regard to hepatic coma and metabolic disturbance.

Now, for (d) -- I want to make sure that --

DR. TALAMINI: Yeah.

DR. MARKS: I've read this ten times.

DR. TALAMINI: It's tricky.

This is Talamini. It's tricky.

DR. MARKS: I'm in agreement with the fact that these systems, with regard to the use of both of these areas that we're talking about, are life-supporting and life-sustaining. I think in the acute poisoning issue, certainly. And they are of substantial importance for preventing impairment of human health or the progression of illness.

However, in the issue with the sorbent hemoperfusion system for hepatic coma -- so I believe that (d) was dealing with both sets of issues. With the issue of hepatic coma, I believe that it's appropriate to maintain them in terms of Category III because they're life-supporting and life-sustaining.

In terms of efficaciousness, I think we've discussed that, so -- I'm trying to decide if -- it says to discuss, and I'm not sure if I'm supposed to agree or disagree.

I agree that both of these agents could have been considered for Class III, that hepatic devices should be maintained in that category.

DR. TALAMINI: Yeah. Thank you, Dr. Marks.

It's tough not to jump to the next question in trying to answer these subtleties.

DR. MARKS: Okay.

DR. TALAMINI: But I think you did a good job.

DR. MARKS: Oh, okay. Thank you.

(Laughter.)

DR. TALAMINI: Dr. Afifi.

DR. AFIFI: I applaud Dr. Marks, and I agree with everything he said.

(Laughter.)

DR. TALAMINI: Dr. Schulman.

DR. SCHULMAN: I'm going to agree with Dr. Marks as well.

(Laughter.)

DR. TALAMINI: It's a good thing you actually got through that traffic, Dr. Marks.

Dr. Dasarathy.

DR. DASARATHY: This is Dasarathy from Cleveland Clinic.

I agree with what Dr. Marks has suggested.

DR. TALAMINI: Okay.

Dr. Agodoa.

DR. AGODOA: I agree with (a), (b), and (c). Actually, I agree with (d) and (e) as well.

DR. TALAMINI: Okay.

Dr. Sjogren.

DR. SJOGREN: Maria Sjogren.

I'm in total agreement with Eric Marks and (a), (b), (c), and (d).

DR. TALAMINI: Thank you.

Dr. Faulx.

DR. FAULX: I agree as well. I don't have anything to add.

DR. TALAMINI: Thank you.

Dr. Simon.

DR. SIMON: Dr. Simon.

I agree with Dr. Marks' evaluation summary.

DR. TALAMINI: Thank you.

Dr. Woods.

DR. WOODS: Karen Woods.

I also agree with (a), (b), and (c).

With regards to (d) and (e), I'm not really certain how my answer is going to be used, what the purpose of these two are with regards to classifying the agents. But I would agree that they're life-supporting or life-sustaining.

And I would like to start with Dr. Marks with every question, if we could, please.

(Laughter.)

DR. TALAMINI: Dr. Gould.

DR. GOULD: Jon Gould.

I'll agree with Dr. Marks as well.

DR. TALAMINI: Thank you.

Dr. Moxey-Mims.

DR. MOXEY-MIMS: Marva Moxey-Mims, NIH.

I agree with (a), (b), and (c).

With regard to (d), I agree that it's life-supporting or life-sustaining. The way the question is worded, it says "or present a potential unreasonable risk of illness or injury," and I don't think it presents an unreasonable risk for the poisoning part.

For (e), I suppose I agree with (e).

DR. TALAMINI: Okay, thank you.

Dr. Coldwell.

DR. COLDWELL: Coldwell.

Showing my good judgment, I'll agree with Dr. Marks.

DR. TALAMINI: Okay.

Dr. Pavlovich.

DR. PAVLOVICH: I agree, (a) through (e).

DR. TALAMINI: Thank you.

Dr. Schwaitzberg.

DR. SCHWAITZBERG: I agree with Dr. Woods that Dr. Marks should lead off the answering.

(Laughter.)

DR. SCHWAITZBERG: I agree with (a), (b), and (c) pretty readily.

And I got to (d) and (e) by looking at intent. It says that it's intended to be. Now, so we don't know whether in coma it actually is life-sustaining; we don't have the data. But the intent is to use it in that fashion, so I'll agree with (d) and (e) as well.

DR. TALAMINI: Thank you.

Ms. Chauhan.

MS. CHAUHAN: Cynthia Chauhan, Patient Representative.

Essentially, I agree with Dr. Marks.

(a), (b), and (c), I agree.

(d), I believe there's a problem. The language disserves the meaning of (d) and causes us all to have questions. So I put disagree because I think the language is disserving, which is, I think, a way of agreeing with Dr. Marks.

And I agree with (e).

DR. TALAMINI: Thank you.

Dr. Rutledge.

DR. RUTLEDGE: David Rutledge.

I agree with (a) through (e).

DR. TALAMINI: Thank you.

Ms. Fennal. Dr. Fennal, sorry.

DR. FENNAL: I agree with (a), (b), (c), and (d).

I do not agree with (e). It may be life-supporting, but life-

sustaining, for how long? So I do not agree with (e).

DR. TALAMINI: Okay, thank you.

So, Dr. Fisher, I think with regard to Question 5, the Panel is unanimous in agreeing with (a), (b), and (c).

I think the Panel probably is wrestling a little bit with the syntax of (d) and (e) but are generally in agreement with both of those statements as well.

Do you wish us to work more with (d) and (e)?

DR. FISHER: No, I actually think they were good. I apologize for the confusion that the wording in (d) may have caused. And I'd like to shout out a special thanks to Dr. Marks.

(Laughter.)

DR. TALAMINI: Okay, Question 6.

MS. GONZALEZ: Question 6. Based upon the available scientific evidence and special controls proposed in Question 3, do you recommend Class II or Class III for sorbent hemoperfusion systems when intended for use in the treatment of drug overdose or poisoning? Please provide a rationale for your final classification recommendation, taking into account the available scientific evidence and your responses to Question 5 above.

DR. TALAMINI: Okay, we'll begin this one with Dr. Fennal.

DR. FENNAL: Mildred Fennal.

Based upon the available scientific evidence and special controls, I would like to recommend that for the use in drug overdose and poisoning, that this classification be Class II.

And my rationale for that is because it does work better with some drugs than other devices.

DR. TALAMINI: Thank you, Dr. Fennal.

Dr. Rutledge.

DR. RUTLEDGE: David Rutledge.

So I'm going to agree with the recommendation for Class II, and the rationale is based upon the data that you presented in your literature review, based upon the special controls that we outlined with the committee previously and based upon the acute use of these products in that setting.

DR. TALAMINI: Thank you.

Ms. Chauhan.

MS. CHAUHAN: Cynthia Chauhan, Patient Representative.

I agree with Class II for the same reasoning that Dr. Rutledge mentioned.

DR. TALAMINI: Thank you.

Dr. Schwaitzberg.

DR. SCHWAITZBERG: Steve Schwaitzberg, Cambridge.

I support the reclassification of these devices for the indication -- this is in the question to go to Class II -- because I think the concerns can be

addressed in the special controls.

DR. TALAMINI: Thank you.

Dr. Pavlovich.

DR. PAVLOVICH: Yes, I agree that for the treatment of drug overdose or poisoning, we can move to Class II based on evidence for safety, efficacy, and the acute nature of the treatment.

DR. TALAMINI: Thank you.

Dr. Coldwell.

DR. COLDWELL: Coldwell.

I agree that the hemoperfusion system should be Class II for treatment of drug overdose or poisoning due to the scientific evidence that's been presented and the safety of the equipment.

DR. TALAMINI: Thank you.

Dr. Moxey-Mims.

DR. MOXEY-MIMS: Marva Moxey-Mims, NIH.

I also agree that for drug overdose and poisoning, these could be Class II with the caveat raised earlier from Dr. Marks about getting more clinical data.

DR. TALAMINI: Thank you.

Dr. Woods. Or I'm sorry, Dr. Gould.

DR. GOULD: Jon Gould.

I agree that this should be Class II for the indications of drug

overdose and poisoning. I believe that the scientific evidence is adequate regarding efficacy and that special controls can be established.

DR. TALAMINI: Thank you.

Dr. Woods.

DR. WOODS: I agree with all the statements that have been made so far, and I believe it should be downgraded to a Class II.

DR. TALAMINI: Thank you.

Dr. Simon.

DR. SIMON: Dan Simon.

I agree in the revision of the hemoperfusion system to a Class II device. The rationale is we've presented discussion and data regarding safety and effectiveness, which I deem is adequate.

DR. TALAMINI: Thank you.

Dr. Faulx.

DR. FAULX: Ashley Faulx.

I agree with moving the hemoperfusion system for drug overdose and poisoning to Class II for the reasons that everyone has presented.

DR. TALAMINI: Dr. Sjogren.

DR. SJOGREN: Maria Sjogren.

I agree with reclassifying on II based on available evidence and the safety controls.

DR. TALAMINI: Thank you.

Dr. Agodoa.

DR. AGODOA: Larry Agodoa, NIH.

I'm going to be a little difficult here. I think the evidence we have is too old, and we need more clinical data for safety and specific labeling for specific drugs, so I think it should stay in Class III until we get the relevant data to support moving it to Class II.

DR. TALAMINI: Thank you.

Dr. Dasarathy.

DR. DASARATHY: Dasarathy, Cleveland Clinic.

I agree with moving it to Class II because I think the special controls that are in place are adequate.

I did hear from Dr. Fisher that there is a way to collect data under Class II as 522, I think is what he said, or some such program that might probably be helpful.

DR. TALAMINI: Thank you.

Dr. Schulman.

DR. SCHULMAN: I agree with reclassifying the hemoperfusion for poisonings, and I think the risks of the procedure were well delineated by the FDA and should be able to be handled by the special controls.

DR. TALAMINI: Thank you.

Dr. Afifi.

DR. AFIFI: Yes, Abdelmonem Afifi.

I had some concerns, as I expressed earlier, about the mixed classification of II and III for the same device, but the responses from the FDA and the eloquent comments by Dr. Woods convinced me that we should separate the two questions. And I do agree that this should be Class II for that purpose.

DR. TALAMINI: Thank you, Dr. Afifi.

Dr. Marks.

DR. MARKS: I concur with moving these devices for poisonings and drug overdose from Class III to Class II, my rationale being the discussion that we had, I believe that special controls with the caveats that the committee has discussed should adequately cover that, and with the additional data and ongoing data collection for potential review at a future date would certainly cover that transition.

DR. TALAMINI: Thank you.

So, Dr. Fisher, with regard to Question 5 [sic], the Panel generally believes that these should be moved to Class II for poisonings and drug overdose with the reasoning behind this being the effectiveness of special controls and the risk/benefit data that we've seen, with one strong dissenting vote, as you've heard, from Dr. Agodoa, for clear reasons.

Is that sufficient?

DR. FISHER: Yes, thank you.

And I would also like just to remind the Panel real quick at this point that with the special controls, whatever goes into effect with one company goes across the board; it would be for all those devices. So when we do talk about things like the addition of clinical data summaries, that would go across the board.

And on the issue of bench control, we try to use -- excuse me, bench testing. We try to use bench testing as a surrogate whenever we can to try to be as un-burdensome as possible to industry.

So just for clarification. Thank you.

DR. TALAMINI: Thank you very much.

Question 7.

MS. GONZALEZ: Question 7: Based upon the available scientific evidence discussed in Question 4 (if any), do you recommend Class II or Class III for sorbent hemoperfusion devices when intended for use in the treatment of hepatic coma or metabolic disturbances? Please provide a rationale for your final classification recommendation, taking into account the available scientific evidence and your responses to Question 5 above.

DR. TALAMINI: Dr. Marks.

DR. MARKS: Brief.

I believe that the current classification of Class III should stand for these devices in the use of hepatic coma and metabolic disturbances. And the basis for that is, is that I do not find adequate scientific data both in terms

of clinical outcome, complication rates, or an identifiable patient mix that allows me to reduce the classification at this point. So they should stay in III.

DR. TALAMINI: Dr. Afifi.

DR. AFIFI: Afifi.

I recommend that the Class III should stand.

DR. TALAMINI: Dr. Schulman.

DR. SCHULMAN: I agree that the Class III should remain intact. And I think the PMAs that are mandated, will be mandated, will go far to clear up some of the fog.

DR. TALAMINI: Thank you, Dr. Schulman.

Dr. Dasarathy.

DR. DASARATHY: Dasarathy from Cleveland Clinic.

I agree that they should stay in Class III, and the rationale is that the data is not sufficient to move it to Class II.

DR. TALAMINI: Thank you.

Dr. Agodoa.

DR. AGODOA: Larry Agodoa, NIH.

I agree with Class III designation. I think we need a lot more data on hepatic coma and metabolic disturbances.

DR. TALAMINI: Thank you.

Dr. Sjogren.

DR. SJOGREN: Maria Sjogren.

I agree with maintaining the Class III because of lack of evidence to move it to Class II.

DR. TALAMINI: Thank you.

Dr. Faulx.

DR. FAULX: I agree with maintaining Class III designation as the benefits have not been shown to outweigh the risks.

DR. TALAMINI: Thank you.

Dr. Simon.

DR. SIMON: This area of hepatic coma encephalopathy, I think it just cries out for more study and more data, so this -- and there's so much we don't know here, so I think Class III is the right designation completely.

DR. TALAMINI: Thanks.

Dr. Woods.

DR. WOODS: Karen Woods.

I agree that this device should remain Class III for treatment of hepatic coma or metabolic disturbances based on my comments earlier. I remain somewhat skeptical about its efficacy, and I believe the data just isn't quite clear, so Class III.

DR. TALAMINI: Thank you.

Dr. Gould.

DR. GOULD: Jon Gould.

I, too, believe that this should remain in Class III for the

indications of coma and metabolic disturbances. And, primarily, the evidence is inadequate. I think when it comes to safety concerns and adequate controls, that we haven't really demonstrated that the device is any less safe than when used for other indications.

I just think that a lot of the morbidity that was observed probably relates to the underlying condition of the patients that received this therapy. But I think, from a risk/benefit perspective, that the benefit is not tangible, and so it should remain in Class III until we have better data.

DR. TALAMINI: Thank you.

Dr. Moxey-Mims.

DR. MOXEY-MIMS: Marva Moxey-Mims, NIH.

I also agree that this should stay as Class III for the issues of the risk/benefit ratio not clearly falling on the side of benefit and more data needs to be gathered.

DR. TALAMINI: Thank you.

Dr. Coldwell.

DR. COLDWELL: Coldwell.

I agree that it should stay as a Class III because we have no definitive data to move it.

DR. TALAMINI: Thank you.

Dr. Pavlovich.

DR. PAVLOVICH: I also agree that it should stay in Class III for

the reasons mentioned.

DR. TALAMINI: Dr. Schwaitzberg.

DR. SCHWAITZBERG: I agree it should stay in Class III.

DR. TALAMINI: Thank you.

Ms. Chauhan.

MS. CHAUHAN: Cynthia Chauhan.

I agree it should stay in Class III for the reasons mentioned.

DR. TALAMINI: Thank you.

Dr. Rutledge.

DR. RUTLEDGE: David Rutledge.

And my recommendation is going to be for it to remain in Class III.

And I do want to state to the manufacturers that the value of your company is determined in part by the quality of data that you're producing on your product, and optimism is not data.

DR. TALAMINI: Thank you.

Dr. Fennal.

DR. FENNAL: I recommend that the classification stay at Class III for lack of availability of scientific data.

DR. TALAMINI: Thank you.

Dr. Fisher, with regard to Question 7, the Panel unanimously agrees that these devices, when used for hepatic coma and metabolic

disturbances, should stay as Class III.

Is that sufficient?

DR. FISHER: Yes. Thank you very much.

I would like to thank the Panel for all of their comments, for their discussion. All of your comments have been duly noted and will be taken into consideration prior to making any final decision on the reclassification.

So thank you very much.

DR. TALAMINI: Thanks, Dr. Fisher.

So I would now like to ask Dr. Rutledge, our Industry Representative; Dr. Fennal, our Consumer Representative; and Ms. Chauhan, our Patient Representative, if they have any additional comments.

Dr. Rutledge.

DR. RUTLEDGE: David Rutledge.

Mr. Chairman, I have no additional comments.

DR. TALAMINI: Thank you, Dr. Rutledge.

Dr. Fennal, any comments?

DR. FENNAL: Mildred Fennal.

No, I have no additional comments.

Thank you very much.

DR. TALAMINI: Okay, thanks.

Ms. Chauhan, any additional comments?

MS. CHAUHAN: Cynthia Chauhan.

No additional comments.

DR. TALAMINI: Thank you.

So I would like to thank the Panel and the FDA for their contributions to this morning's Panel meeting.

Dr. Fisher, final remarks on this section?

DR. FISHER: I think I just did.

But once again, I would like to thank the Panel sincerely for your discussion, for your comments, and that they'll all be considered prior to any final decisions regarding the reclassification of these devices.

So thank you very much.

DR. TALAMINI: Terrific.

So we will now end the first session and break for lunch.

Panel members, please do not discuss or contact anyone about the meeting topic during the break. This includes discussion amongst yourselves or with any members inside or outside of the audience.

The first session of the June 27, 2013 meeting of the Gastroenterology-Urology Devices Panel is now closed.

We will reconvene in this room and open Session II of this meeting one hour from now at 1:15.

Please take any personal belongings with you at this time. The room will be secured by FDA staff during the lunch break. You will not be

allowed back into the room until we reconvene.

Thank you.

(Whereupon, at 12:15 p.m., Session I was adjourned and a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:20 p.m.)

DR. TALAMINI: Let me go ahead and call us back to order, please, for our afternoon session. So it is approximately 1:20, and I would like to call this meeting of the Gastroenterology-Urology Devices Panel to order.

For this afternoon's agenda, the Panel will discuss and make recommendations regarding the proposed classification of implanted blood access devices for hemodialysis from Class III to Class II. The Class III implanted blood access devices for hemodialysis include various flexible or rigid tubes such as catheters and cannulae. The Panel's discussion will involve making recommendations regarding regulatory classification to either reaffirm Class III or reclassify these devices into Class II and comment on whether special controls are adequate to reasonably ensure the safety and effectiveness of this device.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, no conflict of interest waivers have been issued in accordance with 18 U.S.C. Number 208.

We will now hear from the FDA review team.

DR. REID: Good afternoon. My name is Branden Reid, and I am a scientific reviewer in the Division of Reproductive, Gastro-Renal, and Urological Devices.

DR. TALAMINI: Sir, if you could just get the mike a little closer. Thank you very much.

DR. REID: Thank you. Welcome to the FDA Panel meeting for the classification of implanted blood access devices for hemodialysis.

The implanted blood access devices for hemodialysis are one of the remaining pre-amendment Class III medical devices. These devices were originally classified as Class III because FDA believed that the device presented a potential unreasonable risk of illness or injury to the patient. FDA also noted that the implanted blood access device is part of a life-supporting and life-sustaining system and that general controls and performance standards were insufficient to provide reasonable assurance of the safety and effectiveness of implanted blood access devices.

Typically, for Class III devices, a premarket application is required. However, implanted blood access devices are currently marketed through the 510(k) process, which is usually reserved for Class II devices; therefore, we need the Panel's help to resolve this issue. This afternoon, the FDA team will present the clinical evidence for implanted blood access devices and then ask the Panel to weigh in on FDA's recommendation to down-classify them to Class II, continuing the requirement for 510(k)s with the additional special controls, rather than to keep them as Class III and instead requiring PMAs.

Excuse me, sir, this slide is not moving. I'm not sure what

happened.

(Pause.)

DR. TALAMINI: All right. If you want to continue, just based on the slides that don't require a lot of visibility, we all have copies of this, so it's up to you.

DR. REID: Just to continue, the FDA presenting team consists of myself, Dr. Gang Chen, Dr. Carrie Rainis, and Dr. Frank Hurst. Dr. Chen will discuss the methodology used in the systematic literature search and provide an overview of the literature review. Dr. Rainis will review the device adverse event reports, and Dr. Hurst will provide the clinical perspectives and FDA's proposed recommendations for reclassification.

You all have the outline for the presentation. We'll provide a brief device introduction, then the regulatory history and industry response to the 515(i) order; the cleared indications for use; the literature review; device adverse event reports; clinical summary and risks to health; and lastly, FDA's recommendation.

Does everyone have the handout?

DR. TALAMINI: Let me just ask the Panel. Do all the Panel members have a copy of the handout? Dr. Dasarathy, do you have a copy of the handout?

DR. DASARATHY: But I'm sharing it.

UNIDENTIFIED SPEAKER: It's in that gray file.

DR. TALAMINI: Yeah, he doesn't have one. Okay. So we're okay to continue. We all have visibility, if that works. If not, we can take a five-minute break. Yeah, let's go ahead and take a five-minute break, everybody, and we'll reconvene at 1:31. So a five-minute break.

(Off the record.)

(On the record.)

DR. TALAMINI: So we'll call the Panel back into session and thank the tech team for their support.

DR. REID: We apologize for the technical difficulties.

The FDA presenting team consists of myself, Dr. Gang Chen, Dr. Carrie Rainis, and Dr. Frank Hurst. Dr. Chen will discuss the methodology used in the systematic literature search and provide an overview of the literature review. Dr. Rainis will review the device adverse event reports, and Dr. Hurst will provide the clinical perspectives and FDA's proposed recommendations for reclassification.

Here's the outline of the presentation. We'll provide a brief device introduction, the regulatory history and industry response to the 515(i) order, cleared indications for use, literature review, device adverse event reports, clinical summary and risks to health, and lastly FDA's recommendation.

As defined in the current regulation, a blood access device and accessories is a device intended to provide access to a patient's blood for

hemodialysis or other chronic uses. The device includes implanted blood access devices, non-implanted blood access devices, and accessories. The regulation is split between non-implanted blood access devices and accessories in Class II, while implanted blood access devices are in Class III. As a result, the focus today is only on the implanted blood access device for hemodialysis which are implanted for 30 days or more. These are mainly catheters, seen here on the top left, but also include the arteriovenous shunt cannula and tips, seen below, which are rarely used today.

The initial classification panel recommended that both implanted and non-implanted blood access devices be classified into Class II. Following the panel recommendation, FDA published a proposed rule in 1981 recommending the placement of the implanted blood access devices into Class III because FDA believed they had greater risks.

In 1983, FDA formally classified implanted blood access devices into Class III. However, an effective date for the call for a PMA was never implemented, so they were reviewed under the 510(k) process for the next 30 years.

In 2009, FDA published a 515(i) order requiring information on the safety and effectiveness of implanted blood access devices with the intention of down-classifying them. All 15 manufacturers which responded to the request recommended the down-classification to Class II.

FDA published a proposed rule in 2012, under Section 513(e),

proposing the reclassification of implanted blood access devices for hemodialysis from Class III to Class II. FDA also published -- proposed a special controls guidance document. During this period, FDA received four comments on the document, about improving the content or expanding the document beyond the intended scope of the down-classification.

In July of 2012, FDASIA was enacted by Congress, changing the reclassification process from rulemaking to an administrative order requiring panel input, which is why we're here today. Changes also did not allow for finalization of the proposed reclassification and special controls guidance document; therefore, FDA is codifying the special controls.

Here are the cleared indications. Implanted hemodialysis catheters are generally indicated for use in attaining long-term vascular access for hemodialysis and apheresis. They may be implanted percutaneously and are primarily placed in the internal jugular or subclavian vein. Catheters greater than 40 cm are intended for femoral vein insertion.

Additional variations in indications for use statements exist for other implanted blood access device designs such as those for the fully subcutaneous catheters, coated catheters, and AV shunt cannulae.

After considering the information from the reports and recommendations of the Advisory Committee for the reclassification of these devices, along with the information submitted in response to the 515(i) order and any additional information that FDA has encountered, FDA has evaluated

the risk to health associated with the use of implanted blood access devices and determined that the following risks to health are associated with its use: thrombosis in patient and catheter occlusion, or central venous stenosis; adverse tissue reaction; infection and pyrogen reactions; device failure; cardiac arrhythmia, hemorrhage, embolism, nerve injury or vessel perforation; hemolysis; and accidental withdrawal or catheter migration.

Next, Dr. Chen will discuss the methodology used in the systematic literature search and provide an overview of the literature review.

DR. CHEN: Good afternoon. My name is Gang Chen, and I'm an epidemiologist in the Office of Surveillance and Biometrics, Division of Epidemiology. Today I will be presenting the findings from the systematic literature review on the safety and effectiveness of implanted hemodialysis catheters.

I will first provide a brief description of the objective of the review and the methodologies applied. Then I will present the results reported in the literature on safety and effectiveness of implanted hemodialysis catheter use, followed by a discussion of study strengths and the limitations, and finally, to summarize the findings from the review.

The objective of the literature review is to summarize the safety and effectiveness outcomes of implanted hemodialysis catheter use reported in the literature since the year 2000.

A search of PubMed was conducted on March 5th, 2013, using

the terms for implanted blood access devices. All articles are limited to humans, English, and the publication date from January 1st, 2000. Although the implanted catheters have been widely used since the 1980s, there has been an evolution of materials, technology, and the clinical practices over time. Starting after the year 2000, it gives a relative framework for current catheter use, as older data would be less relevant to currently marketed devices.

The initial search resulted in 430 unique papers. Through a first pass of title and abstracts reviewed and the second pass of full-text reviews, a total of 57 articles published after the year 2000 that directly evaluated the safety and/or effectiveness outcomes of the implanted hemodialysis catheter use were retrieved and subjected to epidemiological data extraction, qualitative data synthesis, and analysis.

Among the 57 articles, 36 were studies on various brands of implanted hemodialysis catheter use, of which 27 were single-arm studies and nine were comparative studies. Six papers reported data on a fully subcutaneous catheter, and the remaining 15 papers were case series or case reports. The results will be presented based on these three categories.

First, we'll look at the single-arm studies. All of the 27 studies were observational and conducted in North America or Europe. A total of 3175 patients were evaluated in these studies, with a sample size between 5 and 639. A similar number of males and females were enrolled in 21 studies

presenting the gender information. The mean or median age was between 52 and 78 years old in 20 studies, and two studies were conducted in a younger population.

Regarding the effectiveness, technical success rate, mean blood flow rate, and primary patency rate are the most commonly reported endpoints. Technical success is usually defined as the establishment of hemodialysis access via the access vein with adequate catheter function. The rate achieved was 100% in 8 of the 10 studies reported with this endpoint, while in two other studies the rate was 92.9% and 88%.

This table shows the mean blood flow rate with catheter use. In one U.S. study with 33 patients, the blood flow rate was over 300 mL per minute for all patients. In the five European studies, the mean blood flow rate was between 250 mL and 303 mL per minute.

Five studies reported the primary patency rate at various follow-up time points. Primary patency was defined as the time from catheter insertion until any intervention was performed or the catheter was removed for malfunction or infection. As we can see from this table, in all studies, the primary patency rate decreased over time.

Regarding safety, device-related infection, thrombosis, malfunction, and the device survival were the most common reported endpoints in the 27 single-arm studies. Five studies reported a total of 10.2% to 26% of treated patients with catheter thrombosis. Two studies in Europe

reported thrombosis rates of 1.16 and 1.94 per 1,000 catheter days. Four studies reported catheter malfunction rates of 1.7 to 7.4 per 1,000 catheter days.

Fifteen studies reported catheter-related infection and/or bacteremia rate with the implanted hemodialysis catheter use. The infection rate was between 0 and 3 per 1,000 catheter days in 12 studies, and the bacteremia rate was between 0.3 and 1.77 per 1,000 catheter days in eight studies.

The other complications reported with lower frequencies are listed here.

The Kaplan-Meier device survival rate was reported in five studies. The rates were 62% to 78% at 1 month, 25% to 65% at 6 months, and 13% to 42% at 12 months.

Besides the single-arm studies, there were nine studies that compared the different brands of catheter use. Of the nine studies, seven were conducted in the U.S. and two in Europe. There were three randomized controlled trials and six observational studies. The mean blood flow rate did not differ between catheters in five studies, and no significant differences in infection rates were observed in all studies except one. Overall, the safety and effectiveness rate results reported in the comparative studies for implanted catheters were mostly within the range reported in the single-arm studies.

Next, we will look at studies on a fully subcutaneous venous access device that was designed to overcome the limitations of standard implanted catheters.

Six papers on five original studies were published on this device since the year 2000, with the last paper published in 2006. All of the studies were observational except one multicenter study, in which the randomized controlled trial design was implemented in Phase 1, but later, a non-randomized group was added for comparison in Phase 2.

Although fewer device-related infections and fewer thrombolytic infusions and a higher device survival were observed in the observational phase of the U.S. multicenter study at both 6- and 12-month follow-up when 70% IP was instilled into the subcutaneous pocket as an antimicrobial agent, the complication rates reported for this subcutaneous device in five studies were mostly within what the paper reported for the standard catheters. In one U.S. study and a German study, at least four deaths out of the 70 patients evaluated were reported as contributed to device-related infection.

Finally, there are 15 case series or case reports on complications identified with the standard catheter use. One paper reported 71 patients who were referred to a dialysis access center in the U.S. primarily for a broken clamp or cracked extension tube. The remaining 14 papers reported 18 patients with various complications listed here.

The studies discussed today all focused on the safety and effectiveness of implanted hemodialysis catheter use with the catheter names specified in most of the reports. However, the studies have some key limitations. The major limitations of the single-arm studies include lack of controls, small sample size, follow-up variations, different patient population and techniques in catheter placement. All studies provided Level 4 evidence, which are observational studies without controls.

In some of the comparative studies, the differences in patient selection and other uncontrolled factors between catheter groups, due to the non-randomized design, may have influenced the findings. And some comparative studies had limited power to detect statistically significant differences due to the small number of patients in each catheter group.

For this review, all original reports published since the year 2000 that directly evaluated the safety and effectiveness of implanted hemodialysis catheter use were reviewed, including case series and case reports. However, the literature review has some limitations. First, the review does not include any data published before the year 2000. And, second, as we restricted our evaluation to the data presented in the papers, the publication bias and the bias arising from selective reporting of study findings in a publication cannot be ruled out from this review.

In summary, the published data indicated that technical success can generally be achieved with adequate blood flow rate in most of the

patients placed with implanted hemodialysis catheters.

The catheter patency rate and device survival decreased significantly over time due to catheter-related complications.

And, finally, catheter-related infections, thrombosis, and device malfunction remain the most common complications with implanted hemodialysis catheter use.

This concludes my presentation. Thanks so much for your kind attention.

Next, Dr. Carrie Rainis will discuss medical device reports for the implanted blood access devices.

DR. RAINIS: Good afternoon. I'm Carrie Rainis, and I'm from the Division of Postmarket Surveillance at the FDA.

The Manufacturer and User facility Device Experience database stores medical device reports received by FDA and provides adverse event information involving marketed medical devices.

DR. TALAMINI: Dr. Rainis, I'm sorry, can you get the microphone up a little? That's great, thank you.

DR. RAINIS: FDA medical device adverse event reporting is a passive surveillance system which provides for the following: a qualitative snapshot of adverse events for a specific device or device type; as well as detection of signals for real users in a real-world environment; rare and unexpected events; long-term events; events involving the vulnerable

populations; off-label use; and use errors.

As a passive surveillance system, FDA medical device adverse event reporting is subject to the following limitations: underreporting of events, potentially due to lack of physician awareness; incomplete information; the causality of the events is often not confirmed; there's also reporting biases, which can include reporting practices, media effect, and regulatory actions; the inability to estimate the rate of adverse events due to no denominator data; and, finally, trends in the numbers are limited and should be interpreted cautiously.

Despite these limitations, MDR data provides useful information about the postmarket behavior of medical devices and contributes to, and may be used as a factor towards, FDA's evaluation of the safety and effectiveness of medical devices.

For the purposes of this Panel, MAUDE was searched using the following criteria: the date report received was from January 1st, 1998 to March 24th, 2013. These dates were chosen in order to have 15 years of MDR data to assess any trends over time, especially since the clinical use of some of these devices has declined in the more recent years.

Five product codes for implanted blood access devices for hemodialysis were evaluated individually and include AV shunt cannula, vessel tips, subclavian catheters, implanted catheters, and implanted coated catheters. Additionally, FDA changed product code practices in 1998,

primarily using MSD instead of insertion site-specific procodes such as LFJ.

MDR reports were then reviewed. No reports were found under the procode FKW, which is the vessel tips. Procodes FIQ and NYU, which are the AV shunt cannula and the implanted coated catheters, generated a small number of reports -- less than 50 -- and were therefore individually reviewed. Searches under procodes MSD and LFJ, the implanted catheters and the subclavian catheters, generated a large volume of reports, and therefore approximately 15% of the reports were sampled and individually reviewed. We also looked for additional concerns which were not captured within the risk to health categories.

A text search was performed using the terms "corrective" and "recall" in order to identify any actions taken by manufacturers which were described within the reports.

Using the MAUDE online analysis tool, we assessed the top 100 event types, device problem codes, and patient problem codes.

The following risks to health associated with the use of implanted blood access devices for hemodialysis were identified, as described by Dr. Reid. These risks to health are considered in the MDR analysis.

This graph represents the total number of MDRs reported to FDA under each product code over the time period searched. Note that the date of the event is along the X-axis, rather than the date report received. MSD, which is the implanted catheters, are shown in green. LFJ, the

subclavian catheters, are in blue. NYU, the implanted coated catheters, are in red. And FIQ, the AV shunt cannulae, are in yellow. Reports under MSD and LFJ, there were significantly more reports under MSD and LFJ compared to NYU and FIQ.

Again, there have been no new clearances under LFJ since 1998 because FDA initially procoded catheters based on site and then started using MSD for all implanted catheters. This may contribute to the decrease in MDRs under LFJ over time.

Although the number of MDRs is increasing in recent years, it's important to keep in mind that these numbers are small in comparison to the total number of catheters in use, and that there's a growing awareness of medical device reporting, which may lead to an increase in MDRs across all devices.

A small number of reports were received under the procodes NYU and FIQ. Two devices have been cleared under NYU, the implanted coated catheters, and these are the Palindrome Chronic Catheters and the Palindrome Emerald Catheters. These devices only generated 26 reports since 2006. Therefore, little insight can be offered regarding long-term trends associated with the use of these catheters.

Eighteen MDRs were reported under FIQ, the AV shunt cannula, and the last MDR was received in 2008. There's been a decline in the clinical use and market of the AV shunt cannula with the development of new

catheters, which are now covered under MSD as well as more frequent use of arteriovenous grafts and fistulae.

This graph represents the number of death, injury, and malfunction reports received under MSD, the implanted catheters, over the 15-year time period. Reports which were associated with patient deaths are shown in red. However, it should be noted that the catheter was not necessarily the cause of death. Injury reports are in blue, and device malfunctions are in green.

The number of MDRs received in the early 2000s and the number received between the 2010 to 2012 time period is similar. However, the severity of the events reported has declined with a decrease in injury reports and an increase in malfunctions. The majority of malfunction reports described catheter breaks, leaks, and dislodgments.

The increase in MDRs under MSD since 2008 could be partially explained by recalls under this procode. Recalls under MSD have been initiated due to catheter sleeve, tip, or stylet breakages or connector separations and other packaging and labeling issues. Again, recalls may increase device publicity and therefore increase reporting. However, there are a number of other factors which could have contributed to this increase, and due to the limitations of MAUDE, we cannot establish any direct causes.

This graph represents the number of death, injury, and malfunction reports received under LFJ, the subclavian catheters. Death

reports are again in red, injury in blue, and malfunctions in green. The number of reports received under LFJ is less than half of what we received under MSD, and the number of MDRs has been decreasing over time and remains less than 40 reports per year over the past five years. However, this decrease again could have been influenced by other factors besides a decrease in adverse events, such as changes in market conditions or shifting in hospital practices to devices which are not covered under MSD. Again, there have been no new clearances under this procode since 1998.

Once individually reviewed, each report was placed into 1 of 10 categories along with the risks to health. Note that the number of MDRs listed in the table under MSD and LFJ are for the 15% sampling of reports, and the total along the bottom represents the number that was individually reviewed under each procode.

The majority of reports fell under the risks to health of device failure and include catheter breaks and leaks, followed by the risks to health of withdrawal or catheter migration. No reports for hemolysis were found, and there were only three reports of adverse tissue reactions. Only one was under MSD.

Reports in the other category did not contain sufficient information, or described events which could not be definitively placed into one of the other nine categories. For example, the description simply stated brief phrases such as "removal due to malfunction," "difficult to remove cap,"

or "bleeding led to explant." Individual review of the events within the "Other" category did not raise any new concerns or risks.

In conclusion, the overall review of the MDR data does not raise any concerns associated with the use of these devices which are not already captured within the risks to health for these products.

Next, Dr. Frank Hurst will provide a clinical perspective.

DR. HURST: Good afternoon. My name is Frank Hurst, and I'm a nephrologist in FDA's Renal Devices Branch. I will be providing a clinical summary of implanted blood access devices for hemodialysis as well as discussing FDA's proposed special controls and overall recommendation for reclassification.

There are three main types of vascular access use for hemodialysis: arteriovenous fistulae or native vein-to-artery conduits, which are not subject to FDA regulation; grafts or synthetic vein-to-artery conduits, which are currently regulated as Class II medical devices. Hemodialysis catheters are the third main type, and can be categorized as non-implanted or implanted. Non-implanted are currently regulated as Class II. Today's discussion will address the implanted catheters, which are currently regulated as Class III.

And then of note, implanted catheters are also known as tunnel catheters, chronic catheters, cuffed catheters, or long-term catheters. And for regulatory purposes, long-term means greater than 30 days.

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines described the preferred order of dialysis access, with long-term catheters being the least desirable.

Use of catheters is discouraged because of more frequent complications, unless consistent delivery of blood flow compares with the other types of dialysis access. As a result of these recommendations and other initiatives, there has been increased use of the fistula in recent years, with the majority of established dialysis patients using a fistula for dialysis. Although their use is discouraged, long-term catheters are still frequently used.

In 2011, almost 80,000 patients started dialysis with a catheter, which was 81% of all patients who started dialysis that year. In addition, another 75,000 or 20% of established dialysis patients used a catheter, and nearly 8% of these had used a catheter for greater than 90 days.

The reasons for the relatively frequent use of catheters are listed on this slide. They're used when access is needed urgently or as a bridge to more permanent access. Additionally, they're used in some patients who do not have adequate arterial or venous anatomy to establish a fistula or a graft.

As you have heard in the earlier presentations, catheters are associated with several complications. Acute complications include bleeding, dysrhythmia, embolism, and vessel injury and are generally associated with

the insertion procedure. The risk of chronic complications generally increases over time, and chronic complications include thrombosis, which can be within or external to the catheter, and microbial complications, which can be local or systemic. Mechanical dysfunction can lead to breaks, leaks, or dislodgment, and alterations or reduction in blood flow can lead to hemolysis or inadequate dialysis.

There are several design variations for implanted blood access devices, in addition to the standard implanted hemodialysis catheters. Coated catheters include the addition of anti-infective or antithrombotic coating. Port catheter systems, as can be seen on the image in the lower right, are fully subcutaneous and do not have an external component. Only one of these devices has been cleared but was subsequently recalled by the manufacturer. And the AV shunt cannula will be discussed on the next few slides.

So the AV shunt cannulae were the first vascular access used for dialysis and were first described as the Scribner shunt in 1960. While these were revolutionary at the time, they were still prone to infection, thrombosis, and dislodgment, similar to the catheters we use today. They became less frequently used in the late 1970s and early 1980s as catheters became the preferred temporary vascular access for dialysis.

While rarely used clinically, AV shunt cannula and vessel tips are included in this regulatory classification. And while there are some

differences compared with implanted catheters, FDA believes that the risk profile is similar and believes that it would be appropriate to reclassify these devices to Class II as well. Additionally, FDA believes that special controls can be established to mitigate the risks associated with these devices.

In summary, implanted blood access devices are not the optimal vascular access for dialysis, but they are a life-supporting and necessary treatment option for many patients. And then, while these devices are associated with complications, the adverse effects are well described.

I will now discuss the risks to health and proposed special controls. As you already heard, the following risks to health have been identified for these devices. These risks, along with FDA's proposed mitigations, will be reviewed on the next slide, and the Panel will be asked to comment on these risks to health later.

This slide summarizes the identified risks to health and the proposed mitigation strategies which form the basis of FDA's proposed special controls. I'll just highlight a few examples. For example, thrombosis could be mitigated by performance data, which establishes appropriate priming volumes for anticoagulant lock solutions. Infection could be mitigated by labeling which specifies appropriate insertion site preparation as well as exit site care. Device failure could be mitigated by performance data which demonstrates appropriate tensile strengths of joints and materials. And placement complications could be mitigated by comprehensive insertion

instructions in the labeling.

Based on the identified risks to health, FDA is proposing special controls. We believe that special controls can be established to mitigate these risks to health and provide a reasonable assurance of safety and effectiveness for these devices.

The proposed special controls that FDA believes will mitigate these risks are now included in a proposed order which is available on the *Federal Register* website. FDA has also issued a draft guidance which will provide additional details on how to comply with the special controls, and the draft guidance is also now available on the FDA website.

The next two slides highlight the proposed special controls. I'll just read through these.

Device components must be biocompatible. Performance data must demonstrate that the device performs as intended and must include the following: pressure versus flow, recirculation, priming volumes, tensile strength, air and liquid leakage, repeated clamping of catheter extensions, mechanical hemolysis, and chemical tolerance to repeated exposure of disinfection agents. Performance data must also demonstrate sterility and support of shelf life of a device.

And these are the special controls continued. Labeling must include pressure versus flow rates, priming volumes, recirculation percentages, expiration date, and any disinfection agents that should not be

used with the device. Labeling must also include comprehensive insertion instructions as well as any specific instructions for anticoagulation, management of occlusion, or exit site care. Labeling must identify any coatings and summarize the performance testing for the coatings.

For subcutaneous devices, the recommended type of needle should be described as well as test results on the repeated use of the ports.

Coated devices must include a description of the coating, the duration of effectiveness, and testing to demonstrate performance of the coating.

And the Panel will be asked whether the identified special controls appropriately mitigate the identified risks to health and whether any additional or different special controls are recommended.

I will now discuss the FDA recommendations for reclassification.

So in 1983, FDA noted that these were life-supporting devices and that general controls and performance standards were not sufficient to provide a reasonable assurance of safety and effectiveness. At that time FDA believed that there were not adequate data to ensure their safe and effective use and recommended that these devices be regulated as Class III.

Since 1983, FDA believes that additional evidence has been established to support reclassification to Class II. The devices have continued to evolve over time with upgraded materials and improved insertion

techniques. And the risks are well described, as you have seen, in the literature review and analysis of medical device reports. Additionally, FDA has extensive premarket review experience with clearance of over 200 of these devices.

While not ideal, these devices are effective in that they provide access to the blood for dialysis. In general, their patency decreases over time, and the major safety outcomes are well described, with catheter-related infection and bacteremia ranging from 0.3 to 3.5 events per 1,000 catheter days, and thrombosis ranging from .25 to 1.94 events per 1,000 catheter days.

Of note, high rates of infection have been noted in some studies with the port catheter systems as well as long-term catheters placed in the femoral location. And then other more rare complications are listed as well, although their frequency is less well described.

The analysis of MDRs demonstrated that the number of reports has been relatively stable for recent years. From 2002 to 2012, the number of reports received for MSD, which is the most commonly used product code, ranged from 86 to 359 events, with 310 events reported most recently for 2012. While the denominator for these reports is not known, this number can be considered in the context of the greater than 100,000 catheters used, based on the ESRD network data which was presented earlier.

There have been an increased number of reports for device

malfunctions, but the severity of reported events has declined over time. And FDA believes that the device malfunctions, as well as the more rare serious events such as vascular injury, could be mitigated by the proposed special controls. And, overall, the review of the MDR data did not raise any new concerns that were not already listed in the risk to health categories.

This slide summarizes the previously mentioned benefits and risks associated with the implanted blood access devices for dialysis, and FDA has considered these in their proposal for reclassification.

The FDA rationale for reclassification is presented graphically on this slide, which was also presented earlier today. So in 1983 -- if I can work the pointer here. It's not really showing up well. But, anyway, FDA believed that general controls alone would not be sufficient and that these were life-supporting devices, which kind of takes you to the middle of the slide where FDA did not believe that sufficient information was available to establish special controls and subsequently categorized them as Class III.

FDA now believes that sufficient information is available in order to establish special controls, as discussed earlier. Thus, we would recommend that these implanted blood access devices be regulated as Class II.

In summary, FDA has considered the available scientific literature, medical device reports, premarket review experience, and the benefit versus risk for these devices, and we believe that the available

evidence supports a reasonable assurance of safety and effectiveness and believes that the proposed special controls would be sufficient to provide this assurance. Therefore, we recommend that these devices be reclassified from Class III to Class II.

And this concludes my presentation. Thank you for your attention.

DR. TALAMINI: I'd like to thank the FDA review team for their presentation.

Does anyone on the Panel have a brief clarifying question for the FDA regarding this presentation? Please remember that the Panel may also ask the FDA questions during the Panel deliberations a little bit later.

Dr. Coldwell.

DR. COLDWELL: This is Coldwell.

Did you consider placing the fully implanted port catheter combination as a separate entity, very similar to the way we've talked about the hemoperfusion catheters, the hemoperfusion systems, in the last session? The port catheter system, it's an entirely different animal than the partially exposed tips from the typical dialysis catheter we put in.

DR. HURST: Frank Hurst, FDA.

We did consider that. We felt that it would be better to actually just develop a unique special control for that class of devices, which would specify the additional performance data that would be needed.

DR. TALAMINI: And as I understand it -- this is Talamini -- there was only one and it's now off the market; is that correct?

DR. HURST: That is correct, yes.

DR. TALAMINI: Follow-up, Dr. Coldwell?

DR. COLDWELL: Yes. This is Coldwell again.

Yes, actually, because I've had experience with these total implanted systems, and I know that there seems to be a move towards some of these in the chronic sickle cell disease patients now. And I would encourage the FDA to consider these to be Class III's because the infection problems that I've seen as well as burning at least two access sites every time you put one of these things in, it leads me to believe that the risks are far greater in these than these simple tunneled catheters.

DR. TALAMINI: Thank you.

Dr. Schulman.

DR. SCHULMAN: I'd like to agree with what was just said. I think the Scribner shunts are totally different. And, in addition, another complication -- I'm old enough to actually have worked with them in a fair number of patients -- you have to often re-clamp them with Fogarty catheters. There's a risk of arterial thrombosis with those as well, and I don't think they should be in the same category of totally implanted venous catheters.

The other thing is, in the primary dysfunction, there's a big

drop-off over months. But do you have any data on the secondary patency, whether you could give tPA activates to de-clamp the access? That would be important to consider as well.

The completely subcutaneous catheters, at least for hemodialysis, have fallen out of favor as their use was more disseminated and people had lots of infectious complications as well with those catheters. And I think also the frequency -- or the lack of frequency of the use of the Scribner shunts now really throws it into a different category.

DR. TALAMINI: Other clarification questions? I have one clarification question from the Chair.

The relationship between thrombosis events and patency rates, you address those as separate categories, although obviously they're related, because the most likely cause for one of these devices to not continue to be patent is that it's thrombosed. So how do those relate to one another in your data analysis?

DR. HURST: That's an excellent point. With a lot of the data for implanted catheters, there is overlap for why the catheters would be removed or failed. I mean, I would also point out that if a catheter is infected, it may be removed as well, which would affect the primary patency rate. So it's not just thrombosis. But with the available literature that we reviewed, we were limited to the endpoints that were used in the studies, and that's what we tried to summarize and report as best we could. We tried

to combine as many of the outcomes as we could.

DR. TALAMINI: Okay. And, again, for the Panel, these should be clarification questions at this stage. We'll have time for back and forth with the FDA during our Panel deliberations.

So further clarifications? Dr. Agodoa, I think you had your hand up.

DR. AGODOA: Larry Agodoa, NIH.

My impression is that all catheters are not created equal, and particularly the Scribner shunts that are not being used very much. The lack of data from the MDR doesn't mean that there are no problems with them, right?

DR. HURST: Correct. In the last panel discussion, we discussed the limitations of the MDR reporting, so yes.

DR. TALAMINI: So, again, we had this discussion this morning, in terms of dealing with all of these not as individual devices but as a class. So I guess, again, in terms of clarification questions, that's been your approach in the analysis, is that correct, that you put these together all as one class because of the historical -- the way this is rolled historically; is that correct?

DR. HURST: That's correct, yes.

DR. TALAMINI: Dr. Moxey-Mims, a clarification question?

DR. MOXEY-MIMS: Moxey-Mims from NIH.

My question was on Slide 21 with the literature review. Similar to this issue of patency versus thrombosis, how was catheter-related infection versus bacteremia differentiated in what was placed there?

DR. HURST: A quick comment. Just depending --

DR. TALAMINI: Name, please. Sorry, name, please.

DR. HURST: Oh, I'm Frank Hurst, FDA.

It would depend on the actual study that was reviewed. I believe there were 15 or so studies, and I'd have to look at them individually, but I know they were all not extremely conservative with the definition of infection and bacteremia. The definitions varied. But Dr. Chen may be better suited to answer that question.

DR. CHEN: Yeah, I think the studies I presented in the table shows that we have -- there are about 15 studies that reported these endpoints. And generally they reported the data with infection rate and also the thrombosis, and some of them, actually, they reported the sepsis. As I look at the definition, they're pretty much consistent across the papers, and the infection usually is like more local site, localized events. And bacteremia is more of a systematic disease. You know, it's like not just localized.

DR. TALAMINI: Thank you.

Dr. Schulman, a clarification question?

DR. SCHULMAN: Gerry Schulman.

I believe that CMS counts the HeRO catheters as grafts. Do you

have any data on the HeRO catheters? Is that going to be included in this, or is it a separate thing?

DR. HURST: No, I believe that's considered as an AV graft, which is regulated by a different group.

DR. SCHULMAN: Thank you.

DR. TALAMINI: Dr. Woods, a clarification question?

DR. WOODS: Karen Woods.

I had a question regarding information about the antimicrobial solutions used in a couple of the studies, and in the Panel pack, 6.1.3 talked about sodium oxychlorosene used as an antimicrobial versus isopropyl alcohol, and there were some differences in the infection rates, I believe, in those two studies that looked at the different -- they didn't look at the different antimicrobials; they used different antimicrobials.

And my question is, I assume this is skin cleansing. I don't know. I don't think you would be injecting it into a catheter, but I don't do dialysis, so I have no idea.

Okay, number two, is this a standardized thing now? I mean, is there a better solution that everybody's using now? Are we to be expected to see different solutions, therefore different infection rates on the skin side, related to the use of different antimicrobials?

DR. HURST: Frank Hurst, FDA.

So if I remember correctly, the study that you're referring to

that was referenced in the Panel pack, it had to do with the port catheter systems, and those antimicrobial solutions were actually injected into the pocket. It has a pocket similar to a pacemaker, and the solutions were put into that pocket. For most implanted catheters, we just want to make sure that the labeling complies with the most recent CDC recommendations for preventing infections.

DR. TALAMINI: A clarification question from Dr. Marks.

DR. MARKS: Yeah, this is Dr. Marks from USUHS.

For Dr. Hurst. I just want to clarify something because we're having this discussion about AV shunts. The basis for the categorization of all of these three types of devices within one group was the fact that they're implantable, not what they're implanted into, but the fact they're implantable.

DR. HURST: Correct.

DR. MARKS: Okay.

DR. TALAMINI: Dr. Agodoa.

DR. AGODOA: So did you do any analysis comparing the adverse event rate for each group of catheters, or did you just lump them all together?

DR. HURST: Frank Hurst, FDA.

So for the MDRs, the analysis was by product code, but we didn't do any individual comparisons, for example, for coated catheters

versus non-coated catheters. And that's partially related to the limitations of the MDR database. Like, we don't have the denominator to say how many coated catheters were in distribution versus standard implanted catheters.

DR. TALAMINI: Dr. Simon, a clarification question?

DR. SIMON: Sure. So I just want to understand how this change or potential change would play out in the real world. So if there is a new catheter that comes along next week that's made of a material that the manufacturer claims is going to mitigate the risks that you presented earlier, if we follow through with the FDA recommendation and downgrade the device to a Class II, this new catheter that comes along next week, that then becomes -- because it's a new material, now it's a Class II device or, because it's a new material, it goes back to Class III? Just so I understand how this plays out in the real world.

And a similar question is, it seems like coatings, from chat around the network, are becoming -- and biofilms are becoming an issue. And so people are talking about -- I mean, there are only two coatings out there, but I think there's more coming, and I'm just trying to understand. So how does that play out? Are coatings, a new coating, something we haven't seen on a catheter -- it's an old catheter -- now it's a Class III because of the new coating or does it still stay a Class II? Just help me understand how this plays out in the trenches, so to speak.

DR. TALAMINI: Dr. Fisher.

DR. FISHER: This afternoon's panel is a little bit different than this morning's panel in that we had four intended uses and all the products fell into one bucket. So what we're talking about now, there is the example of a catheter that's not being used as frequently, and Dr. Hurst said, well, we think that we can mitigate that risk with a special control.

What you'll see is that there's a variety of different procodes or types of catheters, and what we will be putting forward is to take all of these and down-classify them to Class II. That's our proposal. But the Panel may suggest that maybe we can't take all of them down. Maybe we have to take special considerations into some of these procodes.

With coatings, then, we start getting into most of these are for antibacterial claims and I'm not sure -- Frank, none of these are coated catheters, right? Are some of these coated?

DR. HURST: For the implanted blood access devices, coated catheters that are intended to be implanted longer than 30 days would be included in that classification.

DR. FISHER: Okay. So we might be able to actually deal with them specifically, instead of putting them into the bucket with the rest of them. It's a strategy that we -- you know, if the Panel were to suggest that, that we would consider it.

DR. HURST: I guess our approach was for the more unique devices, that we would have a separate special control dedicated to those, for

example, the port catheter systems and the coated catheters, where we would request additional information beyond standard implanted catheters.

DR. NEULAND: This is Carolyn Neuland.

I'd just like to clarify something. So right now we're looking at these under 510(k). So just remember that all of them are 510(k)s and under Class III.

So, basically, when a new devices comes in, we look at it and we determine does it have the same intended use? Yes or no. If it is, we move down to the technology. Is the technology the same? Does it raise new types of safety and effectiveness questions?

So we're walking through what we call a substantial equivalence determination. If we find at any point along those ways that we have new types of safety and effectiveness questions or the intended use changes in such a way that it changes the safety and effectiveness profile, we then might say they're not substantially equivalent and they become Class III. So then they fall into the world of PMA-land or they then can come back, perhaps, and ask to be a de novo classification. Those are two options. But they would not be equivalent to the other devices in that classification.

Does that answer your question? And we can ask for data, different kinds of data, along the way, too. We may ask for clinical data on some devices if we're going to decide that they have the same intended use, but the technology is slightly different.

DR. SIMON: No, that's helpful.

DR. TALAMINI: Dr. Fisher, did you have a further comment?

DR. FISHER: No, I'm done.

DR. TALAMINI: Dr. Marks.

DR. MARKS: Yeah, Dr. Eric Marks.

This is very brief. Ma'am, before you leave the podium, what's the threshold to constitute a new device, in light of my colleague's question? I change the cuff on my catheter because I've had migration with the other cuff. Do you then look at the catheter with the new cuff to determine -- since this is one of your concerns, I'm trying to figure, as I guess you are, what's the threshold here. When does the FDA look at this versus what you consider to be an industrial improvement, which is not a substantial difference in the catheter, but potentially, maybe, the new design means you get more migration rather than less?

DR. NEULAND: Carolyn Neuland.

This has a lot to do with our whole substantial equivalence process in 510(k). Companies are allowed to make certain changes as long as they don't sort of raise the threshold of new safety and effectiveness issues. And there's a guidance document that we have out there right now that sort of spells that out. But if they pass that threshold, we then request that they come in with a 510(k). Material changes usually do require a 510(k) because they require new testing that's needed in order to demonstrate that they're

as safe and as effective as the previous version of their device.

So there are a certain line of things they can do without coming in. They document it to file. And then, if they do make a more significant change, they come in to the FDA for that change, and then they do what we call a catch-up 510(k); they catch us up with all the changes they made. Sometimes we find they made a change they shouldn't have made without coming in, but we then sort of evaluate those changes that they had made and document it to file.

So we do go through this on a daily basis when looking at new products and revisions, because I was once told that every year and a half a device changes, and if it doesn't, it's not moving forward in technology. So we expect changes to devices.

DR. TALAMINI: Dr. Pavlovich, did you have a question?

DR. PAVLOVICH: And, again, just a basic clarification. So at the conclusion of the review of these systems with our recommendations, at some point you will then decide these are going to be Class II or III. At that point -- I'm just curious -- the devices that are in use now in the dialysis population, will they then, if they go to Class III, all have to submit a PMA, all be put under scrutiny, and all the developers and all the device companies have to show us great data and all the great data they've accumulated over the 50 years of dialysis? Or not? And then, if it's Class II, we just keep using them and keep getting sort of not particularly great data, even though we

should have great data.

DR. NEULAND: Dr. Neuland. Carolyn Neuland.

Yes, they will have to come in for a PMA. If we decide that you want to call for the PMAs, we keep them in Class III. They would then have to come in on a specified date that we would announce to come in for a PMA, and they would have to have data to stand on their own to demonstrate that they are safe and effective. And the 510(k) level is they're as safe and as effective as the predicate. But a PMA, they stand on their own through data to support their device.

DR. PAVLOVICH: So just as a follow-up. Christian Pavlovich. So from what I read ahead, the sense of the FDA is that that would not be desirable. No more data are really needed. These systems are safe enough. They've been in use, and we really don't want to put the companies through that; is that correct?

DR. NEULAND: We did our evaluation based on the information we have gathered through previous 510(k)s, through MDRs, through the literature, through studies we've already seen. And in putting all of that information together, we feel we have enough data to make that decision to down-classify the devices. So we have based on those things the science.

DR. TALAMINI: But, again, the privilege of the Chair. These should be clarification questions on the presentation. We'll have an opportunity for more back and forth later on.

Dr. Fisher.

DR. FISHER: Ben Fisher, FDA.

And once again, just for clarification, these are already at Class III devices, so we're not talking about moving anything up to Class III. What we're proposing is to move things down to Class II.

DR. TALAMINI: So any further clarification questions?

Dr. Schwaitzberg.

DR. SCHWAITZBERG: This is Steve Schwaitzberg.

Can you reflect the conversation of why you didn't split out the NYUs? When you think about the unmet needs in healthcare today, it is a big portion on reducing infection. And if you take a look at other things like thrombosis, you know there are going to be new infection strategies, you know there's going to be new coatings to prevent thrombosis. And if you think about sort of the national criticisms to the 510(k) process, it's kind of like playing telephone; it's a predicate to a predicate to a predicate to a predicate to a predicate, and what you started off with as a kitty cat, now looks like a zebra.

And can you give us some insight into -- since we just came from a panel where you made a pretty thoughtful split, can you give us some insight into your deliberations, why you didn't split this one? Because, particularly, these are going to be the plastic thing is a plastic thing. But when you start putting all of these add-ons together, I'm kind of --

DR. REID: Branden Reid.

So we think that due to the special controls, we're able to mitigate the risks to health with the special controls. And those should be able to -- you know, for instance, with the coated catheters.

DR. TALAMINI: So if there are -- sorry, Dr. Fisher.

DR. FISHER: Once again, I think we're looking at one class. And you're absolutely correct, I think that there may have been some drift due to the fact that, with comparisons to predicate to predicate to predicate and having devices cleared as 510(k)s, we do have this one procode. I think it's something for us to take into consideration. But as of right now, all of these devices reside in that procode.

DR. TALAMINI: Thank you very much for the presentations and the clarifications. Do you have a further --

DR. NEULAND: Carolyn Neuland again.

I was just going to make one clarification. We do go through that substantial equivalence determination, though, and if we do see something that says a technological change, we can ask for clinical data if we need it. So it does help try to determine whether they are equivalent, and we can throw them out there. So keep that in mind as we go through. But we can have more deliberations later.

DR. TALAMINI: This is Talamini.

They don't just drift all the way to zebra?

DR. NEULAND: They shouldn't drift all the way to zebra.

DR. TALAMINI: So thank you very much for the presentations and the clarifications from the FDA team.

So we will now proceed with the Open Public Hearing portion of the meeting. Public attendees are given an opportunity to address the Panel, to present data, information, or views relevant to the meeting agenda.

Ms. Craig will now read the Open Public Hearing disclosure process statement.

MS. CRAIG: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with any company or group that may be affected by the topics of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at this meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the

beginning of your statement, it will not preclude you from speaking.

DR. TALAMINI: Thank you.

We will now hear from our first scheduled Open Public Hearing speaker. Is Jennifer Yttri here? Jennifer. And once again, you have five minutes.

DR. YTTRI: Thank you. Again, I am Dr. Jennifer Yttri, and I am speaking on behalf of the National Research Center for Women and Families. Our organization does not accept funding from device manufacturers, and therefore, I have no conflict of interest.

Our nonprofit research center includes scientists, medical and public health experts who analyze and review research on a range of health issues. In addition to conducting research and publishing our findings, we provide objective and understandable information to patients, healthcare providers, and policymakers through briefings, CMEs, testimonies, and other materials and formats. We support the FDA's mission to protect public health, and our president, Dr. Diana Zuckerman, is on the board of directors of the Reagan-Udall Foundation and the Alliance for a Stronger FDA.

Implanted blood access devices, we believe, should remain as Class III devices and be subjected to premarket approval because they are a part of a life-supporting and life-sustaining system. When they aren't held to higher standards, we lose four important safeguards: first, the proof of safety and efficacy in clinical trials; second, FDA's authority to require postmarket,

long-term clinical trial safety data and information as a condition of approval; third, FDA's authority to inspect manufacturing facilities prior to approval; and fourth, the FDA authority to rescind approval if the device is later found to be unsafe.

Some Panel members may not realize that under the law the FDA can't require postmarket studies as a condition of approval for a device cleared through the 510(k) process, and if anything goes wrong, FDA can't rescind approval for a device cleared through this process.

Approval through the PMA process could occur based on short-term clinical trials that indicate new devices are safe and effective. And FDA can further require necessary long-term postmarket studies as a condition. FDA can't do that for these catheters cleared as Class II devices.

These implanted devices are left in patients for years, but the long-term data on certain ones are lacking. Even if you think short-term safety data are adequate, I'm sure you'll agree that long-term implants need long-term data to determine the lifespan of these catheters.

Reliance on MAUDE reports to establish the safety profiles of these devices is unacceptable. As you all know, MAUDE reports are voluntary and usually underreport the occurrence of adverse events. MAUDE reports can be used to eventually identify risks associated with a device but do not provide an accurate assessment of the prevalence of each risk. The only way to ensure long-term safety data for these devices is to keep them as Class III.

As a Class III device, the FDA should required controlled clinical studies that directly compare these devices to alternatives such as more temporary devices or surgical blood access techniques. Implanted catheters regulate blood flow, but that flow, as you've seen in the FDA's report, can be irregular compared to other techniques. Though implanted devices can be used quickly for hemodialysis, that benefit alone does not warrant long-term use because better alternatives are available.

Other techniques have become more popular because they avoid device failure and infections that occur with these implanted catheters. In the future, new implanted catheters and cannulae may prove superior to those currently on the market, but that would require clinical trials, and that's why Class III designation is still needed.

We agree that these implanted blood access devices should remain as an option for patients requiring hemodialysis. However, currently available clinical evidence does not prove safety and effectiveness for the number of years these devices are in the human body. Special controls are not enough to ensure the safety and effectiveness for the wide variety of devices included in the down-classification being considered.

Class III devices must be reviewed through the PMA process, which by law is required for implanted life-saving or life-sustaining devices. Without a PMA --

DR. TALAMINI: Fifteen seconds.

DR. YTTRI: -- these devices -- I understand. Without a PMA, these devices will not adequately be tested to make sure they can save lives and that their failure won't kill or seriously harm patients.

Thank you.

DR. TALAMINI: Thank you.

Does anyone else wish to address the Panel at this time? If so, please come forward to the podium, state your name, affiliation, and indicate your financial interest.

(No response.)

DR. TALAMINI: Okay, seeing none, does the Panel have any questions for the Open Public Hearing speaker?

(No response.)

DR. TALAMINI: No questions. Okay, I now pronounce this portion of the Open Public Hearing to be officially closed, and we will proceed with today's agenda. And with the pleasure of the Panel, I think we will go ahead and move to our Panel deliberations and then take a break after that, before we address the questions.

We will now begin the Panel deliberations. Although this portion is open to public observers, public attendees may not participate except at the specific request of the Panel Chair. Additionally, we request that all persons who are asked to speak, to identify themselves each time. This helps the transcriptionist identify the speakers.

So just based upon the presentations and the clarification questions, it sounds as if the issues that need to be deliberated further by the Panel fall into some fairly straightforward categories. One is this issue of whether these all should be dealt with as one category or whether there is more liberty, in a sense, to split some of these out and request that they stay as category III devices.

So I guess I would first perhaps ask the FDA officials or experts to help us with that differentiation between this morning and this afternoon and what the implications would be if the Panel members' opinions were that some of these specific devices, they felt like, should remain category III devices.

Dr. Fisher, can you help us with that? Or one of the other experts.

DR. FOY: Jonette Foy, ODE.

So just to clarify, the Agency has put out our position with regards to where we think these should fall. We've put out both the proposed rule as well as the proposed order, where we believe that they should all be down-classified. We've considered all of the different types, and we've also done an accompanying guidance document that should help facilitate how you could comply with the special controls.

The approach that the Agency has taken is for certain subsets, like the subcu catheters or the coated catheters, as Frank Hurst mentioned

earlier, to put a special control into place for those specific subcategories.

Part of your discussion deliberation today is for you to have just the question that you just asked. If you were to put out a recommendation of a Class III, we would be putting out a call for PMAs. The ramifications would be that the companies would have a preset defined amount of time to come in with a PMA to address those products and to provide sufficient safety and effectiveness information.

The other thing I wanted to put on the table for your deliberations and thought, as well, is to think about if there were maybe additional special controls that you think would be helpful for the subcategories; specifically if you're struggling with the subcutaneous catheters or with the coated catheters, to think about whether or not we fully fleshed out enough or appropriate special controls. Clinical performance data can certainly be a special control for consideration. And I just sort of put that on the table for your dialogue and thought.

DR. TALAMINI: Thank you.

So with that being said, perhaps the Panel, particularly the nephrologists who are more intimately familiar with these catheters and their use -- perhaps there's one category of these catheters that we should take that discussion up more fully, whether additional special controls would make you more comfortable with them going to Class II, as the FDA is currently proposing, or whether that would not be possible and you feel strongly about

category III.

Now, having proffered that, I saw Dr. Schwaitzberg's hand up before I made that comment. So Dr. Schwaitzberg.

DR. SCHWAITZBERG: So taking the comments from our public speaker and the comments that were just made from the FDA, I get concerned that when you start combining things, what you get in the combination is something different than the sum of the parts.

I've spoken about this in other venues, of a story of my former chief who decided to drip penicillin on the mediastinum to control sternal wound infections. Penicillin is harmless. We use it every day. But when you drip it on the heart, it actually causes cardioplegia.

And so you worry about, on these implantable devices that elute potentially drugs that could be in the bloodstream, is the statement from the public speaker accurate, that if we moved a device such as this into Class II with or without the good work of the special controls, that there would be difficulty pulling a potentially dangerous device off the market if we discovered later -- because think of all the drugs. You know, they do 1,000 patients and they still get pulled off the market. There's going to be no 1,000-patient study in any of these devices.

If you find that the combination of these new materials that we're talking about, in the future, produces an unexpected event, what are the limitations of Class II compared to Class III for the protection of public

safety?

DR. TALAMINI: So, Dr. Schwaitzberg, is that a question posed to our FDA experts?

DR. SCHWAITZBERG: Yes, it's a question posed to the FDA. Is there a downside? Because you don't know what you know in the future. If we were to agree and move these devices to Class II, thinking that the special controls would be adequate and then we find something that isn't so good, are we actually limited, as suggested by the public speaker?

DR. FOY: So I will say that, for a 510(k) or a PMA, it's a challenge to get a product withdrawn from the market. Most often, that ends up being the burden that falls on the responsibility of the sponsor or the manufacturer of the product, and through public issues that arise, the product typically will be recalled or removed from the market at the volition of the manufacturer, in and of itself. The Agency does have the regulatory authority, through the Secretary, to actually revoke that, but that, I don't think, has ever been used; so if you want to sort of talk about some of the challenges that you can have with a product that goes through the 510(k) program in comparison to the PMA program.

What happens in the 510(k) program is you are making a substantial equivalence determination. So when you clear a product through the 510(k) program, it becomes what's called a predicate, and then that product can serve as a predicate for other future iterations. I think some of

the technical creep that you were alluding to earlier is what can happen. We can officially rescind a 510(k), but it's not a process that is used very often.

One of the big delineations between a 510(k) and a PMA is, with a PMA you are demonstrating more of an independent demonstration of safety and effectiveness for the product, in comparison to the 510(k) program where you're demonstrating substantial equivalence, which is based upon a reasonable assurance of safety and effectiveness, but it's not necessarily an independent determination. So you are allowed to leverage and pull information from prior iterations of products as part of our information and part of our decision-making process.

And then, as Dr. Neuland went through for the 510(k) program, we actually have an entire process. We have a flowchart. I wish we had it here to show you today. But essentially there are several critical questions that we ask. The first one is (a) is there a predicate, which can be the products that we've already cleared through the 510(k) program? The next critical question is do these two products have the same intended use? If the answer is yes, you walk down to the next critical question. If the answer is no, you can essentially walk them off the 510(k) flowchart, and the product would then be eligible for a PMA review or a de novo review.

The next critical question after intended use is do the products have the same technological characteristics? If the answer is no, the next question you ask is do those technological characteristics raise different

questions of safety and effectiveness? If the answer is no, you can go down and ask for performance data. If the answer to that question is yes, that those devices really do have different technological characteristics that raise different questions of safety and effectiveness, it goes off the flowchart, and then we're back into the PMA or the de novo realm.

So I know I'm going into a lot of regulatory speak here, but the bottom line is it's a little bit of a challenge to pull a product off the market, whether it's a 510(k) or PMA. But we do have subtle differences in the way that products are reviewed initially and the future ramifications with regard -- you know, for a 510(k), it can serve as a predicate.

DR. TALAMINI: Thank you.

Dr. Moxey-Mims, did you have a comment or a question?

(No audible response.)

DR. TALAMINI: Okay, thanks.

Dr. Marks.

DR. MARKS: Yeah, I have a number as we go through this, but I wanted to sort of segment this out. I want to go back to the questions that were raised about the AV shunt cannula and the vessel tips. And I asked Dr. Hurst the issue of how did these all get in, because they're all implantable. I would suggest, for this particular class of device, which I happen to be more than intimately familiar with, that the difference between -- some of the things we're talking about is we're talking about central venous access and

the issues involved in that. What we're talking about is this is arterial and venous access, and there's a difference when you go into the arterial side of anything.

And so I understand they're both implantable, but I think that the risks, precautions, and even the special directions that would come in this, and to who can implant them and how they're maintained, how do you move them, how do you keep them open, these are also things you open up and you get the potential for air leaks. There's a whole series of additional things.

So unless there was going to be a longer list of special conditions attached to this, I'm not sure that it's appropriate to be considering this in the same category as central venous access.

DR. TALAMINI: Thanks. The privilege of the Chair. And your statement was unless there are additional special conditions. I believe that one of the things the FDA would like to hear from this Panel is what those would be. Am I correct, Dr. Fisher?

So Dr. Marks said that unless there was a willingness to add a fair number of special conditions, he would feel strongly that the catheters that are involved in arterial placement would be different. And my comment was that, in fact, the FDA would like to hear what the Panel believes those special conditions should be.

DR. FISHER: Absolutely, absolutely. I think we have presented

some risk/benefits up there and that's -- I think we're going to be asking that specific question to the Panel, like we did this morning. Do you feel that there's adequate special controls that we can put onto this? If we've missed something, we would ask for that input, please.

DR. TALAMINI: Dr. Marks, follow-up?

DR. MARKS: Okay, just a follow-up to this. Does the intensity of the special controls have any impact on whether or not this is appropriately placed in the category of the central venous catheters?

DR. FISHER: What do you mean by intensity of special controls?

DR. MARKS: Okay. Well, we're talking about arterial placement, other kinds of surgical techniques, different maintenance for these types of things. There's a whole list of things that these catheters require in order to be safely used and know about their efficiency, which actually combines some of the things that we now have for the suggested special controls but would extend that significantly.

Is there a prohibition on the extent of a set of special controls before you actually remove this type of device from the general category of implantable devices for the idea of changing the category?

DR. FISHER: In general, I don't believe so. I believe that if a special control can be designed and put into place, then I think that it's fair game.

DR. MARKS: Okay, thank you.

DR. TALAMINI: Dr. Schulman.

DR. SCHULMAN: As I alluded to before, I think they're not all -- the platform devices are not created equal. And I've also a question about the fully subcutaneous catheters as well, because, again, the technique for accessing them are different than the dialysis nurses can access a fistula or a catheter that's coming out of the neck with Luer locks.

You know, when these catheters were tested to see the infection rates, they were studied with people who were very dedicated to accessing them properly. When they became available for use in any unit, the infection rate and the thrombosis rates went way up. And they're not being used all that frequently. And the same thing with the Scribner shunts.

So I'm very concerned about the learning curve in the general population with these accesses, and I think it might be a good idea to split the classification.

DR. TALAMINI: Dr. Fisher, a comment?

DR. FISHER: I would just like to reiterate what Dr. Foy said, and that was that one of the things that you may be able to propose as a special control might be clinical performance data. I'm not sure if that would adequately address your concerns, but I would just like to put it out on the table for consideration.

DR. TALAMINI: Thank you.

Dr. Woods.

DR. WOODS: I want to come back to the biomaterials question and the coating question, similar to what I asked in our training session this morning and Dr. Simon brought up a minute ago.

You know, in my former life as an academician, I did research on biomaterials, biofilms, and coating of biomaterials to try to prevent the buildup of bacterial biofilm in bile for biliary stents. And, you know, the materials, we looked at one material that expanded when wet. We looked at expansion when wet, combined with the coatings of silver and antimicrobials, which quite frankly don't work in the biliary tree and that's why you don't see those stents in our world.

But as I mentioned this morning, if somebody comes up with chemical X that looks awesome in the lab and says, I'm going to coat this similar biomaterial and put it out there, yeah, it's similar. But I don't believe that that equates to equivalent when you coat something with a chemical that you really have no or limited in vivo experience with. And so I would be concerned about allowing that sort of a new coating or, for example, even an expandable -- any kind of biomaterial you could think of, that somebody thinks is the new whoop-de-do for catheters without having more data than just a 510(k) would allow for.

And I guess I'm throwing that out there for discussion, for the FDA's consideration, as to how you would handle that, and again, I guess,

raising the question as to whether or not those sorts of new materials or coatings should be separated out into a different category. And if we did make a rule -- you know, it list things in our list of things that have to be considered -- we would maybe need to say devices that are of different biomaterials that have not been studied or coated with something cannot go through the 510(k), they must go through an alternate pathway.

DR. TALAMINI: Does the FDA have a comment in that regard?

DR. HURST: Frank Hurst, FDA.

I would allude back to the 510(k) decision tree for a technological change such as a new coating that we had never seen before. So if it was a new drug, for example, they may not be able to find a predicate for that device.

And the other comment would be, I guess, in general, without special controls, if there was a different technological characteristic, we would ask for clinical performance data in the 510(k) process. And then, if we think this is going to be a major concern, we could modify the special controls to suggest that we would unanimously need clinical performance data for coated catheters as part of the existing special control or an additional special control for either the coated catheters or the subcutaneous catheters.

DR. TALAMINI: So if I could take the privilege of the Chair just for a moment and ask this question. And, Dr. Fisher, if I'm out of bounds, tell me. Somebody mentioned this morning the example of cardiac stents as a

parallel example of catheters with devices that stay inside the body, and I believe it was mentioned that those catheters are Class II devices with special instructions. Is that also true of the stents that stay in place, and is there any instructiveness or help in that example for what we're deliberating here? And if that's out of bounds, I'm fine to let the question drop.

DR. FISHER: I would have to say -- Ben Fisher, FDA -- that's outside of my purview, my area of expertise. I really can't make that comment. What I would like do is a couple things. Dr. Woods, I think this might help a little bit.

One is you have to identify a predicate. So you have to be compared to something else. So we would be looking at that comparison and taking it through the 510(k) flowchart. The other thing is I really want to try to concentrate on what we have out there right now and not try to dwell too much on what could be down the road.

DR. TALAMINI: Dr. Agodoa.

DR. AGODOA: Larry Agodoa, NIH.

I'm looking at Slides 53 and 54 that Frank presented, where you have the risk to health and then you have the risk and mitigation slide. You mentioned earlier that you didn't do separate analyses for these different catheters, and yet you're coming up with special controls that do not distinguish between these catheters and when they're actually functioning differently. So how can you be sure that the special controls that you have,

lumping all of them together will be equally effective for the various catheters that we are talking about?

DR. HURST: That's an excellent point, and that's why our strategy was to develop unique special controls for the coated and subcutaneous catheters. So there's a list of special controls applicable to all of the implantable blood access devices, but I believe special controls number six and seven address coated and subcutaneous catheters specifically. And, again, I just wanted to reiterate that those could be modified if we thought clinical performance data was necessary, or other performance data or other information for those types of devices.

DR. AGODOA: A follow-up.

DR. TALAMINI: A follow-up question, Dr. Agodoa?

DR. AGODOA: I'm particularly concerned about the Scribner catheters. And like Gerry and Eric, we lived through this, we lived through Scribner shunts, and a lot of what problems we had with them were mechanical, and none of what you're proposing here actually are special controls that are really going to deal with that mechanical problem that we've had with Scribner shunts. So to lump Scribner shunts in with all of these other catheters, I find it difficult to see that this is going -- the special controls you have here are going to be adequate for Scribner shunts.

DR. TALAMINI: So from the Chair. That's a really important point and one that we should bring back with specific answers to the

questions. If we think, in general or for specific catheters, there are additional special controls that would be necessary if these went to Class II, whether or not they go to Class II, I believe the FDA would find value in the expertise of this Panel sharing that. So hang on to that and bring it back when the questions come around, please.

Dr. Coldwell was next.

DR. COLDWELL: This is Coldwell.

I was just perseverating on the completely implanted port catheter combination, in that since the only device that was approved by the FDA was under a 510(k) and then withdrawn, there is no totally implanted device that has FDA approval on the market today. So I would suggest further that we consider that along with the Scribner shunts, anything totally implantable, as a subcategory that we should perhaps consider as a Class III.

DR. TALAMINI: And so perhaps that begs the question of the FDA. If something is off the market, yet approved, and somebody comes along with a new fully implantable dialysis catheter, how would that be managed by the FDA in terms of the predicate device 510(k) process?

DR. HURST: Frank Hurst, FDA.

Even if a device is not on the market, it was cleared and could be used as a predicate device for a new device, although I believe FDA would take the recall into consideration when they're reviewing.

DR. NEULAND: Carolyn Neuland.

Unless you rescind the 510(k), it's still a predicate device. But as Frank started to say, if there's a recall and it showed a certain problem, we might implement some additional testing to make sure that problem is gone with the next device that comes along.

DR. TALAMINI: Dr. Coldwell, a follow-up question?

DR. COLDWELL: Coldwell.

Just about your mandate to do that if it's a Class III device and only highly suggested if it's a Class II. And I have ultimate faith in you, however, trust but verify.

DR. TALAMINI: Dr. Dasarathy.

DR. DASARATHY: Dasarathy from Cleveland.

I'm sorry, this is more of a regulatory clarification for me. If there is a product that is upgraded -- or, rather, downgraded from Class III to Class II, and then there is a new product or a product modification which is using the predicate but appears to be substantially different in terms of what it contains, or physical characteristics or biological characteristics, can that product be dissociated from the other Class II predicates and say no, we would like to have this as a Class III?

The second, I guess, can you downgrade from one category to another one based on clinical data based on new publications and new data?

Thanks.

DR. HURST: So for the first part of the question -- Frank Hurst,

FDA -- I believe what you're describing is what we alluded to before. If it's a new technological characteristic, it could fall out of the FDA paradigm and become a PMA.

DR. DASARATHY: This is Dasarathy again. I'll try to reframe the question.

DR. HURST: Okay.

DR. DASARATHY: Now, if somebody comes to you and says they're using the predicate of a Class II product, but it appears to have significant differences or differences that make it not very similar to what the predicate they're claiming is, except to say that yes, it's an implantable device, nothing else is similar -- so if you're using this -- because the concept of a predicate seems, at least to my understanding, pretty broad. So I could use a comment that this catheter is similar to another catheter. This is like Karen said. You know, you can't compare a biliary stent to a cardiac stent.

So if they're not that different, but they're coating it differently or making it a different product, but they're saying it's a polymer which is similar to what we have used in the other one, how would you address that once you give -- so if there is an option to say that no, this is not, we can always downgrade that specific product alone to a Class III. Then I guess it's a lot easier to think how to answer any other questions.

DR. NEULAND: Each time we look at a new device, if you're a Class II device and you're looking at it in the 510(k) realm, we're actually

making sort of a classification decision. We're looking at are you substantially equivalent to that device? And it can then be classified in Class II. Or are you not? And now you become automatically a Class III device.

So it depends on the differences, the intended use, if it's the same or different. And Dr. Foy just walked you through that again. You look at intended use, and then from there, if it's the same intended use, you move into technological characteristics and you make a judgment based on the predicate device.

We also sometimes use reference devices if there's something -- let's say there's a coating that's been out there forever and we're just going to introduce it to a dialysis catheter. Now, we would sort of assess if it's that brand-new question that throws it into the Class III device or not, but you still are looking at one predicate as you go through that. So we look at that every day, at those changes.

DR. TALAMINI: Dr. Fisher.

DR. FISHER: Ben Fisher, FDA.

One thing that I'm hearing is if it's substantially different, and that's something that we struggle with every time we get one of these applications in. I think if it's substantially different, then it's going to raise questions that could -- like we've been iterating here, it's going to kick it off the 510(k) path, so it's not going to be helpful for that pathway. So it leaves you with one of two others. One is the new de novo pathway, which is if

something is found not substantially equivalent, then we would look at the risk profile. That might be able to come in through a de novo or it might have to go forward. We might make the determination that it's a new device and it needs to go for a PMA. But it's hard to take a generic comment like that. If something is substantially different enough, it might trigger that.

The other thing that I want to put out, you know, these catheters, I think you all have had a lot of experience with it. FDA has had a lot of experience with these catheters, and what we're presenting to you today is what we feel is a good approach, but we're asking you if you feel that it's adequate or not. We think that we have been able to identify a lot of the risks here, and we think that we can mitigate those risks. You may agree, you may not. That's why we're here. We're putting out a proposal out there for you.

DR. TALAMINI: Dr. Schwaitzberg had a question, but before he poses his question, let me begin to push the Panel a little bit towards answering these questions after Dr. Schwaitzberg's question.

Is there someone on the Panel that wants to speak in favor of, or make the case for, all of these devices staying Class III devices? So if there's somebody that wants to make that case, think about it, and after Dr. Schwaitzberg's question, we'll hear from you.

Dr. Schwaitzberg.

DR. SCHWAITZBERG: Thank you, Dr. Talamini.

Steve Schwaitzberg. I'm like halfway there.

So we're talking about can we create adequate special controls to allow these devices to be reclassified into category II? And so they've given examples of the special controls. And so, for subcutaneous devices and coated devices, the concerns about infection don't show up on your list. The converse concerns, the special concerns, concerns about thrombosis, don't show up on the list. Duration of effectiveness is not determined to be clinical. There is no description of long-term follow-up as it relates to the claims.

And even under the risk mitigation of infection, that the risk of infection is mitigated by shelf life labeling and insertion site care, you know, anybody who makes devices, whether it's a new cuff, the devil is in the details. Can bacteria get into the tunnel side? And all of these other little factors. I think what you're hearing in terms of the pushback is general discomfort with these different devices having different characteristics.

So if the subcutaneous device didn't exist and it came to me tomorrow and says, what do you think, Class II or Class III? Compared to what's already on there, I'd go, well, this is different. There's new pocket infections and long-term compatibility things. And the fact that, Dr. Fisher, did you want to deal with the stuff that you got and reclassify it? We're concerned that if it came tomorrow, you know, we wouldn't be -- we'd be comfortable with some things in Class II and other things that are not in

Class III. Is this really your mitigation list or is this sort of your general approach to it? Because, as it stands, it wouldn't be good enough for me.

DR. TALAMINI: Comments from FDA?

DR. HURST: Frank Hurst, FDA.

Excellent point. I did want to reiterate that we still would review all of the information and make a determination. Just because they may include some of the data that we require for special controls doesn't mean it will necessarily get cleared through the 510(k) pathway.

DR. SCHWAITZBERG: Just to clarify. In the previous talk, we talked about clinical data. This list of special controls is not sufficiently specific to answer the question about clinical questions as it relates to performance testing. Just because the sponsor says, we think this will be antibacterial for six weeks, your special control doesn't say clinical verifications of the sponsor's claims. Then the line really blurs between a PMA -- and this was asked early on the other side. One, is it a PMA, and when is it sufficiently rigorous special controls that the difference is immaterial to the sponsor because they're spending money doing studies?

DR. HURST: Frank Hurst, FDA, again.

I think that's an excellent point, and we would certainly welcome any suggestions for improving the special controls that we have that would satisfy your concerns.

DR. TALAMINI: So a point of process. I'm also going to ask the

opposite question, who on the Panel thinks that they all should be Class II? So I'm not predicating one way or the other.

Dr. Fisher.

DR. FISHER: I'd just like to say, regardless if it's 510(k) or a PMA, we're going to be looking for and listing out the type of testings that need to be done. I think the big thing is, when we're looking at 510(k) and PMA, that a 510(k) allows you to compare your device to something else and to prove that it's substantially equivalent. If it's a PMA, it's a standalone. It doesn't necessarily mean that it's going to be safer.

DR. TALAMINI: Yes.

MS. SHULMAN: Hi. Marjorie Shulman, FDA.

I just want to make one point of clarification. It's not that we don't care about what's coming down the road and that we don't want to discuss that here; it's that we can't. We can only go for what we have in-house as of this date. So that's why we're dealing with kind of the bucket we have right now.

DR. SCHWAITZBERG: That's helpful, thank you.

MS. SHULMAN: Thanks.

DR. TALAMINI: Let's see. Dr. Pavlovich, did you have a comment or question?

DR. PAVLOVICH: Christian Pavlovich.

You asked the Panel to start thinking about Class II or III, so I

raised my hand at this moment. It would seem to me that these are all Class III. And that may be not what the FDA wants to hear, but I could support that when that time comes to discuss that.

DR. TALAMINI: Thank you.

Ms. Chauhan, did I see your microphone? Yes.

MS. CHAUHAN: I was going to say something -- oh, Cynthia Chauhan -- that it seems to me, if they have to be in one category and can't be split, that we're looking at Class III. You know, not two categories. I know you can sub-split. And I guess, for me, it comes down to a safety issue for the patients. Then you brought up that the PMA and the five whatever, the five one allows for a comparative study and the PMA does not. Is that correct?

DR. FISHER: Well, we're going to be asking for -- we may be asking for similar data. We may be asking for biocompatibility data for both. What a 510(k) allows you to do is to pick a similar device and compare it, compare your device to that device --

MS. CHAUHAN: Right.

DR. FISHER: -- and prove that it's substantially equivalent.

MS. CHAUHAN: And the PMA does not?

DR. FISHER: A PMA is a standalone. So you're not doing that comparison, but we would still be asking for a variety of testing and safety information.

MS. CHAUHAN: And the other thing that concerns me is, if we

did go with Class II, which I'm leaning more toward Class III right now, you could get so many subcategories with special controls that it seems to me you're defeating your classification.

DR. NEULAND: Again, if you can write a special control for something, then that allows us to put into Class II. And we do try to go for the lowest classification that still allows you to establish reasonable assurance of safety and effectiveness of the product. That is sort of our mandate.

The other thing I just wanted to say, too, that's sort of why we were sort of thinking special controls with Class II. But the other thing is, just remember, if you do want a special control, any device in the classification will have to do that special control. So if you say you wanted clinical data on catheters, every catheter company would have to do a clinical control -- a clinical study for every catheter. If you wanted it just for subcutaneous catheters, then only the people that come in with subcutaneous catheters would have to do a clinical study.

It doesn't mean you might not ask for a study because we find it might be necessary in the other devices, but it would be mandated, then, to require them to do a clinical study before they even come in to us. So just keep that in mind. Whatever special controls you put in place there, for whatever group you're saying it's for, of device types.

DR. TALAMINI: So let -- well, Dr. Fennal.

DR. FENNAL: Mildred Fennal.

I just want to make a comment from the Consumer Representative. We've talked about the product, and I want to take it a little bit to the process and procedure. And I think I would like to say that these devices have been around for quite some time, and if the studies were done adequately, if the information was collected and reported as it should have, it seems to me that there must have been a way that people could have improved the product to cut down on some of the serious kind of reactions that people still have from these devices, which would make it a safety issue.

And then there is the word implant. And I'm saying this because I really am having trouble thinking that we should decrease the class from III to II.

DR. TALAMINI: Any comment from the FDA on that?

DR. HURST: Sorry. Could you repeat the question?

DR. TALAMINI: I think it's probably okay.

DR. HURST: Okay.

DR. TALAMINI: She was mostly stating a strong opinion. So I know there are some other questions out there, but I want to ask if there are Panel members or a Panel member that feels comfortable with what the FDA has put forward, which is that all of these, as a class, go to Class II with special controls. Is there a Panel member that would speak for that, which is, in fact, the FDA's recommendation today for these catheters?

DR. FAULX: Can I just make a comment?

DR. TALAMINI: Sure.

DR. FAULX: Ashley Faulx.

I think for those of us who just don't really get the subtleties -- I appreciate the nephrologists -- it's really hard to me, I think, me personally -- I don't know, as a gastroenterologist, if other people agree that it's sort of hard to come up with that on our own. I don't know. Karen Woods, I don't know if you have a thought. It's just because there are many different varieties even within the subcategories.

DR. WOODS: Do you mind if I respond?

DR. TALAMINI: Sure, please.

DR. WOODS: Karen Woods.

You know, I walked in here after reading all of this, thinking this one's going to be easy, you know, this one's going to be a II. And then I listened to the nephrology experts tell us about the implanted ones and the tunneled one that has the little ports on the outside, and then reassess the data that was presented. And I do see, in learning from them, that there is a difference in these, and I think the data supports that there is a bit of a difference between them.

So I'm having trouble getting my head around thinking of them all the same. Not to mention, I'm still perseverating over my whole concern over the biomaterials and the coatings, which I think you've addressed

somewhat, but I guess I'm still not sure or comfortable -- II or III -- with that, II with special controls. Will that be enough?

So I agree with Ashley. I think that I'm trying to learn from my expert colleagues in nephrology, as to what we should do with four devices in this group as opposed to recommending that maybe they be split.

DR. TALAMINI: I see Dr. Lerner at the podium.

DR. LERNER: Thank you. I'm Herb Lerner. I'm the Deputy Division Director in the reviewing division, and I work with Ben and the whole review team.

I think there is some historical information that we're just not bringing forward, and that's that these devices right now are Class III devices regulated as 510(k)s and that if they were down-classified, there wouldn't be much of a difference in the regulatory pathway because right now they're being cleared through the 510(k) process. There are 200 of these that have been cleared over the last number of years. There are 100,000, if not more, clinical uses every year for patients that need these devices on a daily basis.

So, yes, we see the fact that there are differences in the device types and we think that we can -- with your guidance and some special controls for some of the subsets, we probably could, as we're recommending, keep them in the Class II paradigm. If we were to go to Class III and keep them for PMAs, we would have to go to the Congress and a get whole bunch more people to review all of these PMAs. And we don't have the resources to

do that at the present time, but we would still do it.

Additionally, these companies, if they do have new materials or new characteristics or even the angle of the catheter changes, as we go through the 510(k) flowchart, like Dr. Foy suggested, that may trip the limitations about when we would need either additional data or a PMA or other regulatory pathways to market.

So I think, in general, we've tried to address all of your concerns and then are asking you for specifics about any of the special subsets where you think additional special controls would be needed. So I'm just trying to bucket everything into one sentence here.

DR. TALAMINI: Thank you.

Dr. Fisher, an additional comment? And then we'll go in order of the questions that I see people's hands.

DR. FISHER: Okay, I would just like to put out to the Panel, also, that Dr. Rainis presented some very nice information on the MDR reporting. And actually I hear a lot about the infection and adverse events. If you look at the data, if there was an increase in the data, it was associated with the performance data of the catheter itself -- there it is back up on the screen -- which I think that, once again, we're looking at the malfunctions, injury, and death.

So if you look across all those years, as Dr. Lerner was saying, there's a lot of experience with these catheters over these years. If you look

at this across the years, the blue bars are going down, and I think we're hoping that we can mitigate some of these risks that are associated with the malfunctions of the catheters themselves.

DR. TALAMINI: Did the FDA have a further comment?

DR. RAINIS: Yes. This is Carrie Rainis from FDA. I just wanted to sort of reiterate that point.

So we see here that the injury reports are decreasing and the malfunctions are increasing. But to us, this sort of suggests that the manufacturers are working with us to improve these devices. With the number of recalls under this procode, implanted catheters, and then also within the MDRs, we see references to different corrective and preventative actions that the companies are taking, suggesting to us that the companies are willing to work with us and improve these devices. And then the MDR data showing the decrease in injury reports suggests that this is working.

DR. TALAMINI: Thank you.

Dr. Marks.

DR. MARKS: Eric Marks, USUHS.

Maybe I can help to clarify something here. I think the conundrum that we have is that we're talking about two different issues, I think, as a nephrologist. The FDA is talking about what you just stated, the malfunction of the catheter. Does the plastic break? Does the cuff come off? Does it move? What you're hearing from us is all of the utility data, who puts

it in, how good are they at putting it in, how good are they at maintaining it.

So most of the issues that you have -- and you can look at reports from dialysis units. If they want to improve the quality and the safety of the care, they retrain their people so that you put them in in a standardized way; the other data about central line placements and ICUs that have changed that. You take a look in terms of prevention of thrombosis. What do you prime it with? You know, what do you flush it with? What do you turn it off with?

So I'm trying to get to the issue of, if you're talking about provider performance, which is what we're talking about to a significant degree -- because the longevity of a catheter is more related to how the provider takes care of it than it is, in many cases, to the catheter, which is why I think you see the data there. And I think that the problem in trying to get around this is can you write special controls for a device that influences the way the provider uses it? We sort of talked about that this morning on the Panel. We got concerned, if you have it out there, people will use it even if it's not for what we want it.

So I don't know if that helps the people that had a question about that, but that's really what you're hearing about. My catheters in my -- I say my. That's a malfunction in itself. But the catheters in my unit last a long time because we really take care of them and we train the patients to take care of them when they go home.

So I think that's sort of the performance issue that we get back and forth in here. I don't know if that's helpful, but when we get to special controls, we'll have a discussion about how much you can influence provider activity versus the materials.

DR. TALAMINI: So privilege of the Chair. Dr. Marks, those are really -- that's a really important issue. So the FDA is now up against this. These either have to go -- these either are going to stay Class III and all go through the PMA process or they drop to Class II and these issues are dealt with in special controls.

So with respect to that particular issue, if your belief is the majority of the safety issues boil down to provider issues, then really the question to the FDA is how legitimately can those be executed or effected with these special controls?

DR. MARKS: The Chair's prerogative is absolutely correct. This is Marks again. That, I think, for me is what this comes down to.

DR. TALAMINI: So maybe we could ask our FDA experts to what extent provider behaviors, such as Dr. Marks described, can be put into or effected by special controls. My counter question would be, though, whether you could effect those by going through the PMA process for all of these devices. I mean, my sense would be no.

DR. RAINIS: I just want to add one thing about the MDRs. If you look at the groups that we aligned with the risks to health, we have one

category that may sort of look at how the clinician puts the catheter in, and that was the placement category, and we do not see very many reports within this category. Now, obviously there's all the limitations of MAUDE and maybe people aren't reporting because they don't want to admit that they've placed it wrong or something like that. But compared to the device failures, the placement MDRs were a lot lower. So that might be useful.

DR. FISHER: I was just going to say that regardless of the 510(k) or the PMA process, we're going to end up with the same catheter probably at the end of the day, and it's going to fall back on what Dr. Marks has brought before us. You know, my inkling is to go with the data that Dr. Rainis showed up there, where in fact the blue bars are dropping. So companies are willing to work with us on some things, and something seems to be working there. So hopefully it's the controls that we've put into place.

DR. HURST: I just wanted -- Frank Hurst, FDA -- to address Dr. Marks' question. You know, we can write labeling special controls to include some of the concerns that you raised. And could I make one other point of clarification also?

DR. TALAMINI: Please.

DR. HURST: So the data that we've presented, the MDRs, that reflects the current regulatory process, which again is technically Class III but in practice reflects more of a Class II regulatory process, and we're proposing to add a layer of scrutiny to that with special controls. So actually you see the

adverse effects and the complications we see now. We have developed or proposed to establish special controls to mitigate the concerns that we see to increase the level of regulatory scrutiny compared to what's happening today.

DR. TALAMINI: Thank you.

Dr. Schulman.

DR. SCHULMAN: I think these special controls could be applied to the tunneled catheters. As a matter of fact, there's a recent article in the *American Journal of Kidney Diseases*, listing things that should be done to prevent infections with those catheters. And that could be certainly implemented as part of the special controls. My concern, though, is -- and also the Infectious Diseases Society has just come out with a big position paper on not only dialysis catheters but all sorts of catheters. That's just come out, and again, some of their suggestions could be incorporated.

But my concern is the same thing that we did with the sorbents this morning. It's the fact that the completely subcutaneous catheters and the Scribner shunts are not being used enough to have a good learning curve for the people that are going to do these things, and I really think that that's a big argument for splitting. I would favor Class II for the tunneled catheters, but not for those other two.

DR. TALAMINI: So, Dr. Schulman, just a point from the Chair. I certainly hear you and agree with you, but again, that's a provider issue

similar to what Dr. Marks described, rather than --

DR. SCHULMAN: I understand, but the outcome is the same, regardless, and you're going to have patients that -- if they don't adhere to their infection control, you're going to have people getting the discitis and the carditis. These things exist, and I don't see why the FDA can't -- I know they're dealing with the suppliers of the catheters, but they should be part of the warnings for the practitioners, too, what needs to be done.

DR. TALAMINI: Dr. Dasarathy.

DR. DASARATHY: This is Dasarathy from the Cleveland Clinic.

Yeah, the concern seems to be also that if you leave them in Class III, it will be a regulatory nightmare in terms of logistics for the FDA. I'm more concerned, if we put it in a Class III, what will it do to patient care? This is going to be a pain because -- you know, unfortunately, I don't put in dialysis catheters, but I put in biliary stents. If the same thing was done to biliary stents, I'm going to be thinking, how can I get out of putting this thing in? This is all I'll be thinking because this is just a nightmare for me. So this is going to start affecting, adversely, all patient care.

And this horse has been beaten to death probably 10 times, but we're putting it in a Class III. How are we going to improve or change clinician behavior? That is not the purview of the FDA. This is a job of the AMA. This is a current job of *JKD*'s. It's a current job of CMS. It is not the FDA's job. The FDA's job is really to give you a good product. You make a mess of the

product, it's not the product's fault.

DR. TALAMINI: So, Dr. Dasarathy, do I hear you advocating for Class II?

DR. DASARATHY: Strongly.

DR. TALAMINI: Okay. Dr. Fisher, a comment?

DR. FISHER: Yes. Dr. Schulman, I think your last comment was, could we provide something to help the users? And I think to a certain extent that we can, but only to a certain extent.

DR. TALAMINI: Dr. Woods.

DR. WOODS: Karen Woods.

I just want to ask a real straightforward question to the nephrologists. So if everything were perfect with the cleansing and the care of the four catheters that are listed up here, would you be fine with them being a Class II, or are you saying that a couple of these catheters, even with proper care, you think, are higher risk and therefore should not be considered to be substantially equivalent to the other two?

DR. TALAMINI: So let's ask Dr. Marks that question, and Dr. Schulman.

Dr. Marks.

DR. MARKS: I feel comfortable with the coated and the tunneled. I have a problem with the shunt, and I have very limited experience with the subcu catheters, other than the data I read. But I think

that that's substantially different. That's the reason I asked Dr. Hurst earlier if these are all going in, because we're talking about them being implanted. I mean, that's what got us here, they're implanted. But I think there are substantial differences between the two I just mentioned.

DR. WOODS: Are you talking about under the skin?

DR. MARKS: I'm talking about under the skin and the issues that are involved with that because that's a completely -- I mean, that's a completely closed-off issue. And the AV shunts and these extremities, because of the potential for arterial problems, it's a different class of device, in my mind, because we're in two ends of the circulatory system, not just one.

DR. TALAMINI: Dr. Moxey-Mims, as a nephrologist, do you have an opinion about what Dr. Woods just articulated?

DR. MOXEY-MIMS: I have an opinion based on what I've learned historically. Not having had any personal experience with the Scribner, but hearing horror stories about the Scribner, I would have to defer to my colleagues that have had experience with that device.

DR. TALAMINI: So let me just ask. As a group, do the other nephrologists, in general, agree with Dr. Marks or want to add to the specific question?

DR. SCHULMAN: I would say ditto.

DR. TALAMINI: Okay.

DR. SCHULMAN: He said it perfectly.

DR. TALAMINI: Dr. Agodoa.

DR. AGODOA: I agree with it because, if you look at the column on that board there, the numbers there actually are telling us that not very many people are using it. So it wouldn't be a great loss if that catheter disappears from our armamentarium.

DR. TALAMINI: So let me ask the FDA that question. That's not really a point here, is it, whether it would disappear? I guess if it were a PMA, it would have to be reapplied for, correct?

DR. HURST: Yeah. Frank Hurst, FDA. Correct. But I think it may have already disappeared. The last MDR came in in 2008, but that's beside the point.

DR. SCHWAITZBERG: But somebody can make a new one tomorrow.

DR. HURST: Sure.

DR. TALAMINI: Dr. Schwaitzberg.

DR. SCHWAITZBERG: So I have two questions. Question one would be a comment. Starting with the comment first, if you're going to use the MAUDE database, I love the MAUDE database and I go all around the country giving a complications talk and I pull out of the MAUDE database usually on energy devices and starting fires. And every single doctor walks up to me and goes, I never knew that, number one, I'm supposed to report this stuff, number two, where to report it to, and three, how to report it.

And just like the FDA has started a campaign to stop fires, if you want to be able to bring the MAUDE database to a group like this and then stop apologizing for it -- there is a national campaign to get people who use devices to understand the federal device reporting requirements -- make it easy to do so, so that you can bring some decent data, because, quite frankly, you get up there and you say this data is crap, but this is all we have and it looks pretty interesting, and then you start apologizing for it. So I think there's some public work that needs to be done to get more out of the MAUDE database than what you're currently using.

I'm sensitive to the comment about what it would take to PMA everything. Do you have the breakdown data? We've already sort of determined that, well, if we put the Scribner shunts in a separate category, that's one PMA. What percent of the total devices out there are coated, Scribners, non-coated? Because, quite frankly, if you said to me that 97% of the devices are not coated and not Scribners and all of that, I'd go, fine, send them all to Class II and take these two or three groups and let's talk about whether we should be more stringent.

So we need some forest and trees, because I think when Herb got up there and said, listen, there are 100,000 devices out here and we're not seeing much, you guys are all focused on the complications because we're throwing them in your face, but what we see at the FDA is pretty good behavior in general and that's why we're feeling worried and you're feeling

comfortable. So what's the breakdown on the size of the categories?

DR. HURST: Frank Hurst.

Excellent point. I don't have the actual data. If you just look at the number of clearances, which is not the number of devices in use, there are two coated catheters that have been cleared out of the 200 clearances, and one fully subcutaneous catheter out of the 200 clearances, which is no longer marketed.

DR. SCHWAITZBERG: That's very helpful.

DR. TALAMINI: So, Dr. Agodoa, do you still have an open question?

DR. AGODOA: No.

DR. TALAMINI: Dr. Coldwell.

DR. COLDWELL: Coldwell.

Just from an insertion standpoint, since I'm an interventional radiologist -- I think Dr. Simon can probably back me up on this -- of the catheters that we place, virtually all of them are uncoated, and I haven't put one of these totally implantable devices in in several years. I hope to and actually I will refuse to in the future. But there is a growing movement out there for use of chemotherapy ports in, particularly, pediatric apheresis for sickle cell, to use that total implantable system, which I have questions. But I would say that 99% of what we do would be classified -- could be classified easily as Class II.

DR. TALAMINI: So it feels like we're coming to the end of our deliberations section here, but I would again ask the Panel. We're going to be asked questions individually. We don't necessarily need to come to a consensus. The FDA wants to hear the expertise of the Panel. But you will be asked what the special controls should be if these devices were to be Class II, even if you think they all should be Class III. So please think that through as we begin going through these questions.

It does sort of sound like the group is heading towards a little bit of a consensus, but before we close this session and take a break -- well, Dr. Cooper will have a comment, but this will be the last opportunity for Panel members to directly question the FDA about the issues we've been discussing or about other issues relative to the specific questions we're going to be asked. So if Panel members have those questions, now is the time, but let me ask Dr. Cooper to make his comments first.

DR. COOPER: I just wanted to get a little perspective here. I'm Jeff Cooper, FDA, but a reviewer of these devices for about 17 years, doing the catheters. So I wanted to tell you that we review this as 510(k)s. What we're doing now is trying to put special controls on them to make them even safer. If we go to PMA, we don't have any special controls. So you're again saying to me, make it up, because I've already made it up for 510(k)s, and what we have to review, we based it on what we've seen. And now I'm saying here's the controls we need to put on them to make them even safer.

If we go to PMA, we don't have those controls. So, again, that's kind of back on us to make it up, and that's my concern. When you say we need more control in the PMA, I'm not sure what that control is. So if you all could state what those might be in special controls, either way, that would be really helpful to us to decide what safety we need.

DR. TALAMINI: So thank you, Dr. Cooper.

And I know you have a question, Dr. Marks, but let me ask the Panel --

DR. MARKS: I don't.

DR. TALAMINI: You don't. Let me ask the Panel members specifically, because I've heard this undercurrent a little bit in some of the questions and responses. What areas of special controls are you concerned about that you feel like would need to be added? Now, you're going to be asked that question specifically, but this is the opportunity to have that general discussion as a group and to address further questions about special controls to the FDA.

And perhaps particularly our nephrology colleagues, what categories or areas of special controls do you see missing or that would need to be substantially altered for you to get anywhere near comfortable with the special controls with these as category II devices? And maybe we could ask for that slide to be put back up that had the special controls.

Dr. Agodoa.

DR. AGODOA: So I want to ask this question for the last time. So are we taking off the table splitting these things up so they are not all lumped together? Are we taking that off the table?

DR. TALAMINI: No, no, no, absolutely not. Each of us will be asked that specific question. I just want the group to have the opportunity to air the special controls issue more fully while we're in this section of the deliberations, because I sort of sensed from some of you that there may be large gaps in what you see in the special controls. So I want to be able to address that before we're at the specific FDA questions.

Dr. Simon.

DR. SIMON: Just so I understand, would you like us to then actually go through the proposed special controls -- that would be Slides 56, 57 -- and make particular or specific recommendations? For example, the subcutaneous device special controls they have listed are recommended needle type, test results on repeated port use, and that's -- I mean, that's the special controls that they've -- would you like us to -- I'm just trying to understand the mandate that you've just put forward.

DR. TALAMINI: Yeah, my question would be, if Panel members see big categories missing or substantial gaps in these controls, let's discuss them now rather than when each of us is asked the question about specific controls when we address the FDA -- when we are questioned specifically, because now we can have a back and forth with the FDA about that. When

we get to these questions, we can't. So, again, it's do you see big gaps, categories missing, or specifics, but in particular, big gaps?

MS. CHAUHAN: May I?

DR. TALAMINI: Yes.

MS. CHAUHAN: Cynthia Chauhan.

DR. TALAMINI: Yes, ma'am.

MS. CHAUHAN: Earlier in our discussion, Dr. Schwaitzberg listed some, and I think it would help us if he wouldn't mind relisting those, because I thought that they were to the point that you're discussing.

DR. TALAMINI: Dr. Schwaitzberg, are you willing to take that on?

DR. SCHWAITZBERG: Sure. Only the videotape will prove whether I'm consistent or not.

(Laughter.)

DR. SCHWAITZBERG: I was concerned about the delineation of infection and that the special controls and the risk mitigations are very vague and that they need a lot more specificity, particularly as it refers to looking for clinical data rather than bench top data for things like directive effectiveness of duration, and that there are -- particularly in the coated devices, that the sum of the parts, all of which may have been in clinical use, may be different when you put them all together, than how they function.

I mean, think of products like Seprafilm, which is polypropylene

and -- Seprafilm, which are two approved products and you put them together, does that make you two predicate devices?

So having specifically clinical data that backs up the substantial claims as it relates to infection and thrombosis -- and the same would be true for if a subcutaneous device was to make it. Can you demonstrate that your subcutaneous device is sufficiently resistant to infection just because there's another subcutaneous device out there? So specific clinical information on infection and thrombosis.

DR. HURST: Can I just say something? Frank Hurst, FDA. The slides actually don't have the word-for-word special controls. They would be on your question slides. That may be a better reference.

DR. TALAMINI: Okay. Dr. Marks, I think earlier in some of your comments you had some specific areas that you were concerned about with special controls.

DR. MARKS: Yes. Eric Marks, USUHS.

Part of it is that in looking at the labeling for the following, you talk about insertion and standardizing the insertion piece, so I think that's rather -- there's nothing in here about maintenance, catheter maintenance. I mean, you have a general comment about anticoagulation, but I think it's going to be a matter of does the FDA -- based upon what the provider says and the length of the catheter, do you pack that with heparin or whatever your anticoagulant is? How do you maintain the site? Because there's that

maintenance piece which has a direct role. I don't see any of that in terms of the special control piece, which was the concern I had. You know, it's insertion, removal, and maintenance. And maintenance gets to the point that my colleague was making about infection and thrombosis, because that's when it happens, not usually when you put it in or when you pull it out -- it doesn't matter.

DR. HURST: Yeah. Frank Hurst, FDA. I believe there is a special control pertaining to care of the exit site. If there are additional --

DR. MARKS: There's just a comment that says site care.

DR. HURST: Okay.

DR. MARKS: So we're talking about specificity, and I think that site care is an important issue. But also in terms of, I'm assuming, when you talk about the management of obstruction, you're going to be talking about what the guidance is for the use of thrombolytic agents. I'm trying to determine what you really mean by that. Are you saying that they can be used because it's compatible with this catheter? Are you saying it should be used at a particular time?

You know, you understand the point that I'm making. Once again, it gets to that provider piece. How directive can your guidance be with relationship to the use of a catheter based upon what the manufacturer tells you about its technical specifics? What's the best way to do that?

DR. TALAMINI: Dr. Lerner.

DR. LERNER: Hi, this is Herb Lerner again.

Special controls, as we're writing them today or asking you to comment on them today, are general controls. For each one of these device types that we get a submission for, a 510(k) application, we look at the labeling that the sponsor puts for each individual device itself and look at things like catheter maintenance, wound care, exit site care. So these are just general headings that will be more specific as we look at the labeling for every device that comes in. So we hear you, but we can't put into the general controls specific for each different device type.

DR. MARKS: Can I follow that up?

DR. TALAMINI: Yes, please.

DR. MARKS: Just in terms of --

DR. LERNER: These are special controls, not general controls.

DR. MARKS: Right, but just in terms of that, the question is -- Dr. Hurst alluded to that you go to the CDC for guidance, so it's most -- and we talked about two recent publications about guidance from different societies. Where does the FDA go when you take the general statement about site control? What's your standard to take a look at it and say the information that's here does not appear to be adequate to cover what is now the basis of information we have out there? I'm not going to use standard of care because that's too confining. But where do you go to get that data to say that the information is actually appropriate?

DR. HURST: So Frank Hurst, FDA.

Excellent point. As a reviewer, I would go to the most recent guidelines. I forget the exact name of the guidelines, but there's a conglomerate guideline that includes CDC and the infectious disease associations. So I would verify that the labeling and instructions for use for a specific catheter is written in accordance with those guidelines.

DR. NEULAND: Can I add one more thing? We've even gone down to the detail. If you're putting pictures in, show us you have gloves on. Yeah, that's not aseptic if you don't have gloves on. So we do look at the labeling in that way. Now, whether they change it later, I don't know. We do look at that when we do a review.

DR. TALAMINI: And another question for the FDA. Are there examples where special controls do, in fact, address provider behaviors and placement -- you know, needing to be credentialed, that kind of thing -- or not?

DR. NEULAND: No, we're not actually mandated to be able to say that. That's practice of medicine. We can say that a qualified surgeon who trained to do this should do it. We don't even say surgeon. We have to say a qualified healthcare provider, physician. Yeah, there are certain types of labeling that we can say, but we are somewhat restricted in what we can actually say.

DR. TALAMINI: Dr. Afifi.

DR. NEULAND: We don't want to control the practice of medicine. Actually, while I'm here, the other thing -- this is Carolyn Neuland, by the way. I'm sorry, I didn't say that. But there are also things that we are restricted when we start saying what you can put into the catheter, because that's practice of medicine, too. We might say you need to keep it patent with a proper medical thrombolytic agent, but we wouldn't list ones unless it was only to be used with that.

The caveat to that is we have made catheter companies test the catheter care. When they're caring for them and they're putting various agents on them, we saw breakage. So they do have to test agents and list which ones should be used and shouldn't be used. But that is one of our special controls.

DR. TALAMINI: Dr. Afifi.

DR. AFIFI: I'm wondering if there's another point that we could discuss in this open session, namely, if we are to recommend that some of those devices remain as level III -- maybe the nephrologists can help us. For example, Eric, a lot of thought about subcutaneous devices and a couple of coated devices, are those the ones that could be split off and potentially remain as level III? So any advice on that from the nephrologists would be helpful.

DR. TALAMINI: So I would suggest that it's likely that one or more of our nephrologist colleagues will proffer that in direct response to the

questions that we're about to get to. But if one is willing to proffer that now for further discussion, it wouldn't be a bad thing.

Dr. Schulman and then Dr. Schwaitzberg.

DR. SCHULMAN: I think I said that already, that I would feel comfortable moving the tunneled catheters to Class II. But with regards to Scribner shunts and anything that's implanted subcutaneously, I would not be in favor of that.

DR. TALAMINI: Dr. Schwaitzberg.

DR. SCHWAITZBERG: So I'm trying to get there, Dr. Cooper. Walk us through some history. You said there were two coated catheters, and did they come in by the 510(k) process because they're Class III? And if so, my question is a chicken and the egg problem. If we were to put some significant special controls such as clinical data to show that the expected duration of the antimicrobial effect or the expected duration, how do they achieve the data without an IDE if they're not yet approved for clinical use?

And so part of what I'm trying to understand -- maybe I'm over-thinking this, but what I see, you know, there are two catheters and one subcutaneous, and I'm kind of motivated to say, send them all back for PMAs so you can establish legitimate predicate devices for those few things that we're worried about. The rest of the category will seem to go through pretty seamlessly. What I'm worried is we don't have the predicates because they came in the wrong way through a process that maybe should've been done 30

years ago. And if we don't establish the predicates right to begin with, in these categories we're worried about, we have some of these downstream potential effects that we don't understand.

So tell us how the ones that are currently marketed, what clinical data was required of them, since they seem to have come in on the 510(k) process to begin with.

DR. TALAMINI: Dr. Cooper.

DR. COOPER: Jeff Cooper.

General Hospital had some general use vascular catheters. They cleared a silver-type coating on the catheters. When it came over to the hemodialysis side years ago, we also said that was exactly equivalent, coating-wise, so we applied it to the hemodialysis. From that point we had one other coating come in, which was like a chlorhexidine-type coating. We got that added on.

Our thinking has changed a little bit since that time, and we pretty much put a stop on that, and said if you're substantially equivalent to those coatings, you can also continue in the 510(k) process. If you're different, like you want to put an amoxicillin coating on the catheter, we're saying you've got to show us more data as far as resistance. You've got to show us that it's effective and you've got to do some testing on this.

The question is, do you need strict clinical testing or can you do this on the bench, dip it in a plate and say hey, it was great at resisting

colonization for four hours? Is that enough to put in the labeling, or do we need strict clinical testing that says exactly what it will do? So that's another question we have to struggle with.

DR. SCHWAITZBERG: In the 510(k), how did that pass the intended use test, since what you're describing is some pretty short-term use and what we're talking about today is intended longer-term use? How do you make the leap?

And I guess that's sort of what are those kinds of things that are troubling me, because I know about other 510(k) devices that were approved in minimally invasive surgery. So they got used and there was no data. And then when they did the clinical trial, claims that were made by the companies and the marketers, they're all wrong and the process didn't work. So those are the kinds of experiences that scar us.

DR. COOPER: As far as if somebody would come in with amoxicillin and say I want to put it on the catheter, is that the idea?

DR. SCHWAITZBERG: No, the same stuff, the silver. You have a catheter that's for short-term use, and now we're talking about it in dialysis, which is long-term use. How do we know that that intended use test should have been the stopping point that would have generated a PMA right then and there?

DR. COOPER: That's a judgment decision on our part when we look at it and say is this raising new safety questions? I mean, is the fact that

it's on a short-term catheter for 30 days, that may be used a little bit longer, sufficient to be used in a catheter that may be four to six months? And we may come across and say, hey, it's the identical coating and we've got some experience on it. We know what the safety is and we're fine. If you're crossing over into, hey, let's add another component to that, we may pull back and say no, let's get a little more data on this, which is where we're at this point.

DR. TALAMINI: So point of the Chair. We're getting dangerously close to a necessary bathroom break here, and I was kind of hoping we could get to the end of this section and be ready to have the specific questions. I know Dr. Rutledge had a question or a comment.

DR. RUTLEDGE: David Rutledge. I'll try to make this brief.

There are two slides in here that are very compelling to me, Mr. Chairman. Number one is Slide 22, the single-arm study, and 27, that last bullet where it says Kaplan-Meier device survival rates, and they're like all over the place and not very good the longer you look at it from one month, six months, and 12 months. And I look at that and I say, number one, there is huge variability, and then, number two, there seems to be an unmet medical need out there. And then I would say I'd like to see more clinical data to help me understand this for patients, for physicians, and their family members.

The other piece with Slide 36 where it talks about the MDR rates, if you look at those green bars, we've been sort of neglecting the green

bars a little bit because we're focusing in on the low blue bars. For our complete data, the three largest green bars are the last five to eight years. It occurs in the last three years of the data. So I look at that and then I say, you know, there is something going on from a malfunction standpoint that manufacturers need to know about to be able to make better products for patients and physicians.

So there are a couple of clinical data elements, as I'm looking at this, that I'd like to see relative to a special control or requiring it in a PMA to address, and one would be you would intuitively think that disease severity is going to affect device durability. I mean intuitively that makes sense, and I know we've seen that in some of the devices that I've worked with and you've seen also. So I'd like to have more information on the target population and the disease severity where these devices are being placed, as an example. So there are some clinical data I'd like to see to be able to understand all of this variability in this device survival, or lack of.

And the second thing would be predictors of disease, a device malfunction or patency. With all the data that can be collected, it serves the patient and the physician well, and the manufacturer, to know what the limitations are and what to be careful about, about how these devices should be made. And so we should have better information on what are the predictors that are device malfunctions, especially with it being as huge as it is over the last five to eight years. And also patency rates.

And the final thing would be, as I was listening to this provider issue, which we deal with with PMAs a lot, in terms of learning curves, we should require, if we think this is an issue, the manufacturer to provide FDA with information on learning curves, as an example, or at least engage in those discussions to be able to provide data at the time of a submission, as an example.

DR. TALAMINI: Comments from the FDA, particularly on your blue bars?

DR. RUTLEDGE: And the green bars, really.

DR. TALAMINI: I'm sorry, the green bars increasing recently. These are still small numbers compared to the number of catheters being put in, correct?

DR. HURST: Frank Hurst, FDA.

I agree. I think it's important to keep in mind that one malfunctioning device can lead to 50 reports, which would vastly throw off the ranges typically reported. So at least for me, personally, it's hard to, I guess, see these numbers as a concern.

DR. TALAMINI: So I think at this point we should take a 10-minute break. And what I would ask the Panel to do -- Dr. Fisher.

DR. FISHER: If I could, there has been a lot of talk about special controls. We have three slides that we've put up that dealt with special controls. And so that you don't see this for the first time, maybe during the

break you could look in the question package because, once again, we talk about special controls, and there's about three pages that give yet some additional special controls. Sometimes I think it's additional examples that may help to answer some of your questions. But just so that you don't see it on the first -- the first time that you see, it's not up on the screen. Maybe if you could just look at that during the break.

DR. TALAMINI: Right. So what I'd like to do is take a 10-minute break but keep this part of the discussion open so that when we come back from the break, we'll have a last opportunity to discuss in this open forum some of these issues. So it would be wise, if you have a moment, to look at those special controls. With that said, we will close the session now and come back in 10 minutes. Thank you.

(Off the record.)

(On the record.)

DR. TALAMINI: It is now 4:18. Let me call the Panel back to order.

And, again, we're still officially in the section, the session of the meeting where we are deliberating as a panel about these issues. And I would ask the Panel one last time if there are other questions to bring up amongst ourselves or to the FDA before we go the specific questions that we'll be answering.

(No response.)

DR. TALAMINI: And I'll give you a moment. Doesn't sound like it.

Okay, at this time, let us focus our discussion on the FDA questions. Copies of the questions are in your folders. I want to remind the Panel that this is a deliberation period among the Panel members only. Our task at hand is to answer the FDA questions based on the data in the panel packs, the presentations we heard today, and the expertise around the table.

With this said, I would ask that each Panel member identify him or herself each time he or she speaks to facilitate transcription.

So please show the first question.

DR. REID: Questions to the Panel.

Question Number 1: FDA has identified the following risks to health for implanted blood access devices for hemodialysis based on the input of the original classification panel on January 23, 1981, review of industry responses to the April 9, 2009 515(i) order and the June 20, 2012 proposed rule, review of marketing applications, the Manufacturer and User facility Device Experience (MAUDE) database, and FDA's literature review:

- Thrombosis in patient and catheter, catheter occlusion, or central venous stenosis. Inadequate blood compatibility of the materials used in this device, blood pooling between dialysis sessions, or turbulent blood pathways could lead to potentially debilitating or fatal thromboembolism.

- Adverse tissue reaction. Inadequate tissue compatibility of the materials used in this device could cause an immune reaction.
- Infection and pyrogen reactions. An improperly sterilized device could cause a skin or bloodstream infection.
- Device failure. Weakness of connections or materials could lead to blood loss or device fragment embolization.
- Cardiac arrhythmia, hemorrhage, embolism, nerve injury, or vessel perforation. Improper placement into the heart or blood vessel could damage tissues and result in injuries.
- Hemolysis. Turbulence or high pressure created by narrow openings or changes in blood flow paths could cause the destruction of red blood cells.
- Accidental withdrawal or catheter migration. A catheter's cuff may not allow adequate ingrowth from the surrounding subcutaneous tissue, which could cause the device to dislodge or fall out with subsequent blood loss.

a. Please comment on whether this is a complete and accurate list of the risks to health presented by implanted blood access devices for hemodialysis.

b. Please comment on whether you disagree with inclusion of any of these risks, or whether you believe any other risks should be

included in the overall risk assessment of implanted blood access devices for hemodialysis.

DR. TALAMINI: So let me prevail upon Dr. Schulman, if I could -- I'm sorry -- to be the first to answer this question, as one of our nephrology representatives. And then we'll go clockwise around the table.

So is the list of complications complete?

DR. SCHULMAN: This is Gerald Schulman.

It is, but if you're going to include the Scribner shunts, arterial thrombosis would be a risk.

DR. TALAMINI: Okay. So complete with the addition of the Scribner shunt?

DR. SCHULMAN: Yes. I mean, if you're going to include them in the reclassification, then yes. The Scribner shunt, because it's in an artery, if it gets clotted and you have to declot it, the thrombus can go into the artery.

DR. TALAMINI: And, specifically, the risk is arterial thrombosis?

DR. SCHULMAN: Both venous and arterial. Venous is less of a problem, but arterial is the real thing. You have to -- it's tricky, because you sort of have to -- sometimes you push in and pull out with a syringe and you get the clot out, but sometimes it will go into the arterial circulation.

DR. TALAMINI: Okay.

Dr. Dasarathy.

DR. DASARATHY: I think that the three pages of risks are pretty

comprehensive.

DR. TALAMINI: Okay, thank you.

DR. DASARATHY: Or the controls, I'm sorry.

DR. TALAMINI: Okay.

Dr. Agodoa.

DR. AGODOA: I think, for Scribner shunt, separation and bleeding. In other words, exsanguination is also a real threat for Scribner shunts, and that should be included in here.

DR. TALAMINI: Okay, thank you.

Dr. Sjogren.

DR. SJOGREN: I think the list is complete.

Thank you.

DR. TALAMINI: Dr. Faulx.

DR. FAULX: Ashley Faulx.

I don't have anything to add to the list.

DR. TALAMINI: Dr. Simon.

DR. SIMON: I think there are small things that can be added to the list, but in aggregate, I think it's complete.

DR. TALAMINI: You don't want to add any of the small things?

DR. SIMON: Well, I mean, to even -- they brought some up, you know, in some of the talks. Initially, there was, I think, a case of cancer occurring as a site placement. I personally have seen paroxysmal emboli as a

result of catheter placement with stroke. But I sort of feel like, again, there are such low incidence of events and this list, sort of, is pretty comprehensive.

DR. TALAMINI: Okay, thank you.

Dr. Woods.

DR. WOODS: Karen Woods.

I would agree with the list being comprehensive and agree with my nephrology colleagues who have added a few things that sound reasonable to me as well.

DR. TALAMINI: Dr. Gould.

DR. GOULD: Jon Gould.

I would agree that this is a complete and accurate list.

DR. TALAMINI: Dr. Moxey-Mims.

DR. MOXEY-MIMS: Based on, again, working with folks who have had experience with Scribner, I would agree with adding potential for exsanguination if Scribners are going to be part of this.

DR. TALAMINI: I'm sorry, exsanguination?

DR. MOXEY-MIMS: Yes.

DR. TALAMINI: Okay.

Dr. Coldwell.

DR. COLDWELL: Coldwell.

I agree that this is a reasonably comprehensive list. The only

addition I would make, other than the ones that have already been made, is to say, under infection, to say not only an improperly sterilized device, but also that improper accessing of the device can cause an infection.

DR. TALAMINI: Okay, thank you.

Dr. Pavlovich.

DR. PAVLOVICH: I have nothing to add. I agree.

DR. TALAMINI: Dr. Schwaitzberg.

DR. SCHWAITZBERG: Since there may be other AV devices in the future, or this one, there are steel syndromes associated with putting these in. I put one in as a resident, and we had to ligate the downstream vessel the same way you do with even a surgically created shunt.

And is anaphylaxis included in the adverse tissue reaction? Because if you put drugs on these devices, whether it be silver, chlorhexidine, or whatever, and you put it in again, because they might need a device in the future, there could be a sensitization. And so, since we're putting all these in one big category, some of these will have essentially drugs combined onto the device, and so I would say that anaphylaxis should be a possible consideration for those device drugs.

DR. TALAMINI: Thank you.

Ms. Chauhan.

MS. CHAUHAN: Cynthia Chauhan.

I agree.

DR. TALAMINI: Dr. Rutledge.

DR. RUTLEDGE: David Rutledge.

This also includes the FDA literature evaluation that was performed, and in those slides, you actually present death from a device from an infectious process occurring with the device. So I don't know if death would be a piece of this or not. It was in your slide.

DR. TALAMINI: Okay. Thank you, Dr. Rutledge.

Dr. Fennal.

DR. FENNAL: Mildred Fennal.

In regards to comments on whether this is a complete, accurate list, I defer to the experts. And I do not disagree with anything that's in there.

Thank you.

DR. TALAMINI: Thank you, Dr. Fennal.

Dr. Marks.

DR. MARKS: Eric Marks, USUHS.

I would add the issue about, in particular, for air embolization with relationship to the Scribner shunts, and I concur with the concerns of my colleagues about premature separation and significant bleeding associated with that.

And also in line with the infection and pyrogen reactions, it's not just simply the device or the access to the device, but it's the maintenance of the site at the point of entrance that I think also ought to be

included as a potential risk, the skin area at the point of entrance.

Other than that, I believe the rest of the list is complete.

DR. TALAMINI: Dr. Afifi.

DR. AFIFI: I have nothing to add.

And thank you, Mr. Chairman, for not having me as the first one to answer this question.

(Laughter.)

DR. TALAMINI: You noticed.

Dr. Fisher, with regard to Question 1, the Panel generally believes that this list is accurate, but as heard, hopefully in the transcription, there are Panel members who believe there are additional elements that should be either added or strongly considered.

Is that adequate?

DR. FISHER: Yes, it does. And we've captured those additions.

Thank you.

DR. TALAMINI: Question 2.

DR. REID: Question 2: For medical devices considered to have moderate risk such that general controls alone are not sufficient to mitigate the risks to health, special controls are often developed. FDA believes that the following special controls can adequately mitigate the risks to health for implanted blood access devices for hemodialysis and provide reasonable assurance of safety and effectiveness:

(1) Components of the device that come into human contact must be demonstrated to be biocompatible. Material names and specific designation numbers must be provided.

(2) Performance data must demonstrate that the device performs as intended under anticipated conditions of use. The following performance characteristics must be tested:

(a) Pressure versus flow rates for both arterial and venous lumens, from the minimum flow rate to the maximum flow rate in 100 ml/min increments, must be established.

(b) Recirculation rates for both forward and reverse flow configurations must be established, along with the protocol used to perform the assay, which must be provided.

(c) Priming volumes must be established.

(d) Tensile testing of joints and materials must be conducted.

(e) Air leakage testing and liquid leakage testing must be conducted.

(f) Testing of the repeated clamping of the extensions of the catheter that simulates use over the life of the catheter must be conducted, and retested for leakage.

(g) Mechanical hemolysis testing must be conducted.

(h) Chemical tolerance of the catheter to repeated exposure to commonly used disinfection agents must be established.

(3) Performance data must demonstrate the sterility of the device.

(4) Performance data must support the shelf life of the device for continued sterility, package integrity, and functionality over the requested shelf life that must include tensile, repeated clamping and leakage testing.

(5) Labeling must bear all information required for the safe and effective use of implanted blood access devices for hemodialysis including the following:

(a) Labeling must provide arterial and venous pressure versus flow rates, either in tabular or graphical format.

(b) Labeling must provide the arterial and venous priming volumes.

(c) Labeling must specify the forward and reverse recirculation rates.

(d) Labeling must specify an expiration date.

(e) Labeling must identify any disinfecting agents that cannot be used to clean any components of the device.

(f) Any contraindicated disinfecting agents due to material incompatibility must be identified by printing a warning on the catheter.

(g) The labeling must contain the following information: comprehensive instructions for the preparation and insertion of the hemodialysis catheter, including recommended site of insertion, method of insertion, a reference on the proper location for tip placement, a method for removal of the catheter, anticoagulation, guidance for management of obstruction and thrombus formation, and site care.

(h) The labeling must identify any coatings or additives and summarize the results of performance testing for any coating or material with special characteristics, such as decreased thrombus formation or antimicrobial properties.

(6) For subcutaneous devices, the recommended type of needle for access must be described, stated in the labeling, and test results on repeated use of the ports must be provided.

(7) Coated devices must include a description of the coating or additive material, duration of effectiveness, how the

coating is applied, and testing to adequately demonstrate the performance of the coating.

a. Please discuss whether you agree that the proposed special controls are adequate to mitigate the risks to health for implanted blood access devices for hemodialysis and, in addition to general controls, provide reasonable assurance of safety and effectiveness.

b. Please discuss whether you disagree with inclusion of any of these special controls, or whether you believe any other special controls are necessary.

DR. TALAMINI: Thank you.

So, obviously, this is one of the key questions of the afternoon, and I think it would be appropriate to begin with our star, Dr. Marks, and go counter-clockwise on this question.

DR. MARKS: Yes, sir.

I want to start -- instead of taking -- I want to get to a point that's come up before. I want to go to Number (6), talking about "For subcutaneous devices, the recommended type of needle for access must be described."

Being that that seems to be the only special control for this specific agent, I think that that's inadequate because it's more than the needle for access in the labeling. It has to do with the issue about placement

and -- you know, the tests -- and I'm not quite sure about what the test results and repeated use means of the port.

If we're talking about whether or not the port maintains its functional stability so you can keep sticking it without lead, or the issue of having the transfer of the skin and the subcutaneous tissue to make entrance into this on multiple times, and that's clinically related data. And it was part of the reason why the device was withdrawn, in part, because it would go in sterilely and then after two or three sticks be infected.

So I think that that's an inadequate listing, and as I pointed out, it would have to be more detailed if it was going to fit into the (2) issue in terms of having additional clinical data about how the device is going to be accessed, appropriate guidelines for that, what had to be monitored in relationship to that.

DR. TALAMINI: So that's really an answer to Part b. You believe that that should be included as special controls?

DR. MARKS: Yeah. I believe that -- I'm trying to add to the addition of the special controls, and I was using that as an example because, as Number (6) stands, I can't accept that as a special control which is adequate, so I disagree with what they have there in those suggestions. It does get to be, as to why --

DR. TALAMINI: Okay, let me ask for a time out and take the privilege of the Chair to ask Dr. Fisher for his comment.

DR. FISHER: Thank you very much.

The intent here was that (1) through (5) would be included in (6). So those items would be captured there, so I apologize that that wasn't clear. But all of (5) that had to do with insertion placement, those things would carry over for (6). So I agree the way that (6) stands by itself right now is inadequate.

So I just want to thank you. I just wanted to clarify that.

DR. TALAMINI: Thank you, Dr. Fisher.

DR. MARKS: I would also like to, in area (5), we talk about the compatibility of disinfecting agents and the exposure of the catheter.

Dr. Hurst also mentioned, I think, there needs to be some data about what we pack the catheters with for anticoagulation or antibiotic processes to make sure that we have a knowledge as to how the materials will respond to anything essentially that we put down the catheter, and that's not really clarified here, just the disinfectant piece.

I also think that the issue about site care should be expanded in terms of data included about what can be referenced to the appropriate wound care guidance by any of the sources that were mentioned by Dr. Hurst when he gave his presentation.

As for the remainder of the issues here, I don't find anything else that I would change. But the caveat being that the subcutaneous catheters, I believe, are a separate item, as I bill the same thing for the shunts

because many of the issues here deal with the catheter, but they don't deal, as Number (5) does, with the specific issues about the maintenance of the catheter, and that's where I would consider that additional detail would be required if that agent was included in the change of category.

DR. TALAMINI: So I don't want to put words in your mouth, but are you saying that with respect to (a), that these special controls are acceptable --

DR. MARKS: Yes.

DR. TALAMINI: -- for all the catheters with the exception --

DR. MARKS: The exception of subcutaneous and Scribner shunts.

DR. TALAMINI: Thank you.

Dr. Fennal.

We'll go counter-clockwise.

DR. FENNAL: Mildred Fennal.

I concur with the gentleman who just listed all of the items that should be there.

DR. TALAMINI: Thank you.

Dr. Rutledge.

DR. RUTLEDGE: David Rutledge.

You know, I'm really wanting to get there, and my first round here, I'm going to say I concur and I agree with (a) and I don't disagree in (b),

although I have this nagging desire for more clinical information. So for whatever that's worth.

DR. TALAMINI: So let me clarify, Dr. Rutledge. With respect to (a), are you saying that the special controls would be acceptable --

DR. RUTLEDGE: Yes.

DR. TALAMINI: -- for the entire class, which is slightly different from what --

DR. RUTLEDGE: Yeah, I would say with the caveat that he gave about the two devices that he mentioned a few minutes ago.

DR. TALAMINI: Okay, great. Thank you.

DR. RUTLEDGE: And then I don't disagree with the others, although I do have this lingering desire for manufacturers to submit clinical data. But maybe we'll talk about it in another context later.

DR. TALAMINI: Okay, thank you.

Ms. Chauhan.

MS. CHAUHAN: Cynthia Chauhan.

I concur with Dr. Marks' presentation and remarks.

DR. TALAMINI: Dr. Schwaitzberg.

DR. SCHWAITZBERG: Steve Schwaitzberg.

I concur on Items (1) through (5). I want to separate out the subcutaneous devices for a second, in a bit.

And for the coated devices, I think that with these devices in

particular, manufacturers are going to be tempted to make claims that they're either antithrombotic or that they're antibacterial.

So I'm okay with the comments as written, although they're no different than what's in the slides, thank you. But that there has to be some demand for the manufacturers to support the claims after these devices go into use because I've been lost in this chicken-and-the-egg thing, you know, if you require them to do 10,000 patients before you can get approval, they'll never do the device.

So I've been trying to work my way forward on this and to me, the way to move forward with these coated catheters is to ask the manufacturers to be able to substantiate the claims that are associated with these coatings, which are thrombosis and infection.

DR. TALAMINI: So driving towards clarity, you would add a third. So we've heard Scribner shunts --

DR. SCHWAITZBERG: Well, I would add to Number (7) that -- and the special controls for coated devices will be post-approval studies to support the claims made by the manufacturers.

DR. TALAMINI: Got it. Thank you.

DR. SCHWAITZBERG: And in terms of the subcutaneous devices and the Scribner shunts, I don't think these controls are going to be adequate. You know, we're only talking about two devices; they're both off the market. I would reboot both of them so if people bring devices forward,

they're going to start from scratch.

DR. TALAMINI: Thank you.

Dr. Pavlovich.

DR. PAVLOVICH: I agree with Dr. Schwaitzberg. Pretty much (1) through (5) I'm good with.

And I can't comment much about Scribners and subcutaneous devices, but I would defer to my nephrology colleagues like Dr. Marks.

And I think coated devices, I think the perfect setting to study that would be, sort of, a post-approval study rather than an onerous study that could not be performed easily. My overarching feeling is we do need more studies, we do need more data. The idea that these are safe, these tunnel catheters are safe and efficacious, is not really true. I mean, they're as safe and efficacious as we want, which is to allow dialysis for a few months before the fistula graft gets put in, so definitely, at this point, I would agree with what's been said.

DR. TALAMINI: Thank you.

Dr. Coldwell.

DR. COLDWELL: Coldwell.

I would agree, again, with Dr. Marks and with Dr. Schwaitzberg. With those two caveats, I would agree with both (a) and (b).

DR. TALAMINI: Thank you.

Dr. Moxey-Mims.

DR. MOXEY-MIMS: Marva Moxey-Mims, NIH.

I also agree with the statements here and the caveats added by Drs. Marks and Schwaitzberg. I think the postmarketing issues would be really, really helpful for this.

DR. TALAMINI: Dr. Gould.

DR. GOULD: Jon Gould.

I agree. I don't believe that the Scribner shunts and the subcutaneous shunts necessarily belong in here. I don't believe that the controls, as described, are adequate for those two categories.

And I agree with what Dr. Schwaitzberg said about the clinical piece, although I am concerned about saving this -- it's a balance between saving this for postmarket, demonstrating clinical outcomes that correlate with proposed benefit to whatever they've coated the catheter with versus the desire to really have something on the market be proven efficacious and how onerous will that make a new product to get to market.

I don't know how we could write a special control in a way where these products -- once they are out there, they really needed to back up their claim to stay on the market. Because I just see what's happened in other areas, like I think hernia mesh is a great example. There are a million things out there that are tweaked a little bit differently, and the end of the day, we just have 50 different kinds of mesh without any real benefit.

DR. TALAMINI: Thank you.

Dr. Woods.

DR. WOODS: Karen Woods.

So I think (1) through (5) are adequate. However, what's missing, I believe, in (1) through (5) are actual recommendations for good medical practice for maintenance and access, day-to-day access, of the catheter. I really don't think there's anything listed in here that I see that has to do with that. Most of the things in Number (5) deal with catheter performance and with placement, initial placement.

So I think per the discussion earlier, it appears that reduction of infection and maintenance of catheter patency has a lot to do with individual variations in medical practice. So I think adding an (h) that would say something to define good medical practice standards for catheter cleansing, maintenance, et cetera, would be very important. And then the existing Number (h) on 5 is actually -- I think could be combined with Number (7), which talks about the coated devices.

On Number (7), I think coated devices must include a description of the coating or additive material. I think that should be a description and purpose of the coating or additive material and so on.

And I very much agree with Dr. Schwaitzberg and Dr. Gould regarding needing some more information to support the claims because you do hear a lot out in practice, the reps coming in and telling you all these wonderful things about some of these coatings and whatnot, but I've always

been a little uncomfortable that they're substantiated in the real clinical world. So whether you do it as postmarketing or request it up front, I don't know what the best way to do that is within the purview of the FDA, but I think we need to be very cognizant of making a very strong statement that expects these companies to provide data to support their claims, so that may need to have an extra sentence worded in there.

And I think similarly about the biomaterial. You know, if you're going to come to us with a new biomaterial, we're going to expect you to provide strong data as to why this should be a 510(k) as opposed to a PMA.

And then deferring to the information of the expertise of my nephrology colleagues, I think I would agree with them on not including the subcu devices or the Scribner shunts in these recommendations.

DR. TALAMINI: Thank you, Dr. Woods.

Dr. Simon.

DR. SIMON: Sure. Dr. Simon.

I agree with the recommendations (1) through (5).

On the subcutaneous devices, I think they should be carved out, or at least this is not adequate, even -- Dr. Woods alluded to one issue which was brought up in the materials you sent us. I don't know if any companies even go down this road, but the subcutaneous devices, underneath the skin, the port needed to be locked with an antiseptic, whether it was isopropyl alcohol or chlorhexidine, which I kind of remember

this. This was put in a syringe, 1 ml syringe, with a 25-gauge needle which had to be placed through the skin to touch the top of the port but not puncture the port and fill that subcutaneous space with this antiseptic.

So this management of the port, this isn't even addressed in your subpoint (6), and so if a company chose to go down this, those issues would certainly need to be placed in here, so I would carve that out. Same with the Scribner shunt.

On the coated devices, I second the comments my colleagues have made. One thing that I would encourage the FDA to think about is, you know, there ultimately may be some surrogate markers, surrogate endpoints that companies can look to on these coatings that may assist in terms of like, their development, their testing, and so it's just sort of think about what might be some of these -- and I know some are sort of floating out there -- what might be some of these surrogate markers that companies or developers could look to or talk to you about to assist in these coatings because there is a vast unmet need which clearly is brought out in all the complications and issues that were discussed earlier.

Thank you.

DR. TALAMINI: Dr. Faulx.

DR. FAULX: Ashley Faulx.

I agree with my colleagues regarding (1) through (5).

I guess, regarding the other, sort of, subtypes of devices, I was

somewhat swayed by Dr. Cooper discussing the fact that by -- I know we're not talking about class in this question, but by being able to put out controls for these devices versus just leaving them in Class III might be a better way of dealing with these devices versus putting them back in Category III. So I guess I would defer to Dr. Marks and, sort of, his thoughts about how using his changes for the controls for the subcu devices probably best addresses those.

DR. TALAMINI: Dr. Sjogren.

DR. SJOGREN: I agree with the controls with the caveats from Dr. Marks and Dr. Schwaitzberg.

DR. TALAMINI: Thank you.

Dr. Agodoa.

DR. AGODOA: Larry Agodoa, NIH.

For (a), I agree with (a) except for subcutaneous and Scribner shunts should be excluded from this.

And if you go to (b), any other special controls necessary for Scribner shunts, specifically anticoagulation, haven't helped. And you have to put other special controls in place for that, but all of these were tried, such as exit site care to prevent infection and anticoagulation, surgical construction to guard against separation. None of these worked. So I think it can be a nightmare to include Scribner shunts and, as Eric said, subcutaneous as well.

DR. TALAMINI: Thank you.

Dr. Dasarathy.

DR. DASARATHY: I agree with all the comments that have been made.

The only question I have is for (5)(g), where it says the detailed instructions. Actually, I think we need to move with the times. It is possible that the manufacturers can not only write them in a paper form, but they can possibly put up a video on their website which will probably be a much better training site, so that if there are upgrades, they can upgrade the videos and say that this is what we found.

This would help the site maintenance, it would help the placement issues, all the questions that the nephrologists are talking about. It looks like more of an operator issue than a material issue that can be addressed by a video much better than any form of text, so I don't whether it can be included in this, whether it can be enforced or not.

DR. TALAMINI: Thank you.

Dr. Schulman.

DR. SCHULMAN: This is Gerald Schulman.

I agree with the points (1) through (5). I would exclude, again, the subcutaneous devices as well as the Scribner shunt.

With respect to (5)(g), I think something that was mentioned by one of the FDA people about, saying that a physician trained in the catheter placement needs to be put on the recommendations. There should be some

information about repair kits, if the Luer locks get cracked or if the clamps come off, there are repair kits for these catheters; that should be mentioned.

And then, also, I think some language about the barriers for the tunnel catheters in between uses should be recommended.

And I agree with the comments made by others about the coated catheters.

DR. TALAMINI: Thank you.

Dr. Afifi.

DR. AFIFI: I agree with the comments made by all the panelists, and I have no additional ones to make.

DR. TALAMINI: Thank you.

So, Dr. Fisher, it's a good thing that we have transcription.

With respect to Question 3 [sic], the Panel generally does seem to have reached consensus that with respect to (a), the special controls are not adequate for two sets of devices, the Scribner shunts and subcutaneous devices. And with respect to coated devices, the special controls may well be adequate with some additions.

And then with respect to (b), you heard a cornucopia of suggestions regarding adding to or modifying the special controls as they exist.

Is that sufficient?

DR. FISHER: I would like to thank the Panel. That was one heck

of a question, and I really appreciate all of your comments and your feedback.

I know that no sales rep would ever exaggerate a claim on a device, but I think that it underscores the importance of making sure that we collect the data that we need to be able to substantiate the claims that they're making. And I think we're cognizant of that, and we will make sure that we put an effort of that within our special controls. That's our intent.

And so thank you to the Panel, and I'd also like to say it was nice having Dr. Marks back in his position, so thank you.

DR. TALAMINI: Question Number 4.

DR. REID: Question Number 3.

DR. TALAMINI: Oh. Number 3, I'm sorry. I lost track.

DR. REID: That's all right.

Section 513 of the Food, Drug, and Cosmetic Act states a device should be Class III if:

I. Insufficient information exists to determine that general controls are sufficient to provide reasonable assurance of its safety and effectiveness or that application of special controls would provide such assurance, and

II. If, in addition, the device is life-supporting or life-sustaining, or for a use which is of substantial importance in preventing impairment of human health, or if the device presents a potential unreasonable risk of illness or injury.

Regarding requirement I above, please discuss the following:

a. Whether you believe that the application of general controls, required for all medical devices, are insufficient to provide a reasonable assurance of safety and effectiveness for implanted blood access devices.

b. Whether you agree or disagree with FDA's view that the application of general controls, and the special controls proposed in Question 2 above, are sufficient to provide reasonable assurance of safety and effectiveness for implanted blood access devices.

Regarding requirement II above, please discuss the following:

c. Whether you believe that implanted blood access devices for hemodialysis are life-supporting or life-sustaining, or for a use which is of substantial importance in preventing impairment of human health, or present a potential unreasonable risk of illness or injury.

Please note that the question above refers to Class III eligibility only; the next question will ask for a final recommendation for device classification.

DR. TALAMINI: So for the record, the reason I said that was Question 4 is that that's the way it was labeled in the book here.

Perhaps I could prevail upon Dr. Moxey-Mims, as one of our

other nephrologists, would you be willing to take the first crack at this and then we'll go clockwise?

DR. MOXEY-MIMS: Sure.

DR. TALAMINI: Thank you.

DR. MOXEY-MIMS: Marva Moxey-Mims, NIH.

So with regard to Part a, I agree that the general controls are insufficient, and with regard to Part b, I agree that addition of the special controls with all the caveats that were stated when we discussed Question 2 would be sufficient for assurance of safety and effectiveness of the implanted access devices.

DR. TALAMINI: How about (c)?

DR. MOXEY-MIMS: Sorry, forgot about (c).

So for Part c, indeed, I think we agree that blood access devices for hemodialysis are life-sustaining, if not life-supporting, and are of substantial importance in preventing impairment to human health.

DR. TALAMINI: Thank you.

Dr. Coldwell.

DR. COLDWELL: Coldwell.

Part a, I agree.

Part b, I agree with the carve-out of the two implanted devices.

And Part c, yes, that is true.

DR. TALAMINI: I'm sorry, the carve-out of the Scribner shunts

and the subcutaneous devices?

DR. COLDWELL: Yes.

DR. TALAMINI: Thank you, Dr. Coldwell.

Dr. Pavlovich.

DR. PAVLOVICH: Christian Pavlovich.

I also agree with (a), general controls are not enough.

Under (b), I'm still not sure if I agree or disagree that special controls will be adequate for the tunnel catheters. And I would also exclude the subcutaneous and Scribners. I would sort of defer to FDA. I think it's clear that we need to maximize safety and effectiveness of these short- to long-term catheters, and if the special controls are a better way to do that, great. If Class III classification is a better way to do that, I would tend to vote for whatever they think is a better way to go. And unfortunately I don't think I have enough information still to make that decision.

And regarding (c), I think clearly these are indeed life-supporting/life-sustaining and prevent the impairment of human health.

DR. TALAMINI: Thank you.

Dr. Schwaitzberg.

DR. SCHWAITZBERG: Steve Schwaitzberg, Cambridge.

General controls are insufficient.

Special controls are sufficient except for subcutaneous and Scribner shunts.

And these are life-sustaining and life-supporting.

DR. TALAMINI: Thank you.

Ms. Chauhan.

MS. CHAUHAN: Cynthia Chauhan.

I agree with Dr. Schwaitzberg, especially about excepting the Scribner and the subcu.

DR. TALAMINI: Thank you.

Dr. Rutledge.

DR. RUTLEDGE: David Rutledge.

With those three points, Number 1, I agree.

(b), I agree with the caveats.

And (c), I believe.

(Laughter.)

DR. TALAMINI: Okay.

Dr. Fennal.

DR. FENNAL: Mildred Fennal.

With (a), I agree.

With (b), I defer to the experts.

And with (c), I agree that it's life-supporting and life-sustaining.

DR. TALAMINI: Thank you.

Dr. Marks.

DR. MARKS: Eric Marks, USUHS.

I agree with letter (a).

I agree with letter (b) with the exception of the Scribner devices and the subcutaneous devices. I don't feel that the special controls are adequate to address the multiple issues with them.

And for (c), I agree that these are life-sustaining, life-supporting, and substantially important devices.

DR. TALAMINI: Thank you.

Dr. Afifi.

DR. AFIFI: Rather than restating what Dr. Marks said, I'll just say I believe exactly as he does.

DR. TALAMINI: Thank you.

Dr. Schulman.

DR. SCHULMAN: I agree with (a) and (c), and I agree with (b) with the exception of the Scribner shunts and the subcutaneous catheters.

DR. TALAMINI: Thank you.

Dr. Dasarathy.

DR. DASARATHY: This is Dasarathy.

I agree with (a) and (c), and I agree with the recommendations of the nephrologists for (b).

DR. TALAMINI: Thank you.

Dr. Agodoa.

DR. AGODOA: Larry Agodoa, NIH.

I agree with (a) and I agree with (c); and (b), if you take out subcutaneous and Scribner, I'm fine with it.

DR. TALAMINI: Dr. Sjogren.

DR. SJOGREN: Maria Sjogren.

I agree with (a), (b), and (c), with the caveats expressed by Dr. Marks.

DR. TALAMINI: Thank you.

Dr. Faulx.

DR. FAULX: Ashley Faulx.

I agree with (a) and (c), and I defer to my nephrology colleagues for (b).

DR. TALAMINI: Dr. Simon.

DR. SIMON: Dr. Simon.

I agree with my nephrology colleagues on (a), (b), and (c).

DR. TALAMINI: Dr. Woods.

DR. WOODS: Karen Woods.

I agree with (a) and (c) and agree with the nephrologists on (b).

DR. TALAMINI: Dr. Gould.

DR. GOULD: I agree with Dr. Woods.

(Laughter.)

DR. TALAMINI: So, Dr. Fisher, we do have consensus on Question 3. The Panel agrees with (a) and (c) and agrees with (b) with the

exception of the Scribner shunts and subcutaneous catheters.

Is that adequate?

DR. FISHER: Yes. Thank you very much.

DR. TALAMINI: Okay, on to Question 4. Or no. Oh, Question 4. Yeah.

DR. REID: Yes, 5 on your sheets but 4 on here.

Based upon the available scientific evidence and special controls proposed in Question 2, do you recommend Class II (Special Controls) or Class III for implanted blood access devices for hemodialysis? Please provide a rationale for your final classification recommendation, taking into account the available scientific evidence and your responses to Question 3 above.

DR. TALAMINI: So, Dr. Agodoa, could I prevail upon you to begin, and we'll go in a counterclockwise direction?

DR. AGODOA: Larry Agodoa, NIH.

I would agree with Class III for Scribner and subcutaneous. And Class II, reclassification of Class II, for the other two devices based on the comments that we made previously.

DR. TALAMINI: Thank you.

Dr. Dasarathy.

DR. DASARATHY: I agree with what Dr. Agodoa says, and I think that they should stay as Class II.

Thanks.

DR. TALAMINI: Thank you.

Dr. Schulman.

DR. SCHULMAN: I agree that the tunnel catheters, both types of tunnel catheters, should be reclassified to II, and that the other two, the subcutaneous and the Scribner shunt, remain in Class III.

DR. TALAMINI: Thank you.

Dr. Afifi.

DR. AFIFI: I agree that -- the reclassification into Class II for all of the devices except for the Scribner and the subcutaneous, which should remain as III.

DR. TALAMINI: Thank you.

Dr. Marks.

DR. MARKS: Eric Marks, USUHS.

I agree that the tunnel catheters, both coated and uncoated, should now be placed in Class II but that the Scribner and the subcutaneous devices should be maintained as Class III devices.

DR. TALAMINI: Thank you.

Dr. Fennal.

DR. FENNAL: Mildred Fennal.

I'm going to recommend that all of the catheters remain as Class III, and I would just like to give a rationale because it's very difficult to

have questions asked in a certain way for you to make a decision and then you start separating out because that's not what they asked. And I don't know how you can approve something if you don't have all of the facts in front of you. So I'm recommending that they all stay in Class III.

DR. TALAMINI: Okay, thank you.

Dr. Rutledge.

DR. RUTLEDGE: David Rutledge.

I'm going to say for Class III, I'm going to agree with the experts with the Scribner and subcutaneous devices as Class III, and the rest as Class II.

DR. TALAMINI: Thank you.

Ms. Chauhan.

MS. CHAUHAN: Cynthia Chauhan.

I have felt like a ping pong ball during this discussion, going back and forth between Class II and III, but what I finally come down to is the importance of continued, uninterrupted access for patients. And I think to achieve that, we need to move to Class II for everything except the Scribner and the subcu, otherwise my understanding is it will become a nightmare.

And actually, functionally, the devices are already treated as Class II, and we are simply trying to get the paperwork, if you will, to reflect the activity of the FDA.

So Class II for everything except Scribners and subcu.

DR. TALAMINI: Thank you.

Dr. Schwaitzberg.

DR. SCHWAITZBERG: Steven Schwaitzberg, Cambridge.

If you look at the history of these devices, the panel recommendations were ignored 30-something years ago.

So I'd like to provide some rationale. If we're going to treat all of these devices in one class, then I'm going to agree with my colleagues at the end of the table, that they would have to stay in Class III. The Scribner shunt is dangerous, and you can't possibly treat it the way you would treat a tunnel catheter if it was in a different category.

So if you have to lump it all together, then you have to go to the lowest common denominator of patient safety, and if they go into a single category, they should all be in Class III because the Scribner shunt is going to drag the whole class of devices down.

That said, my recommendation would agree with the colleagues that the Class II recommendation for the other devices other than the subcu and Scribner would be fine, but you have to be willing to split the categories; otherwise, I would keep them all as Class III.

DR. TALAMINI: Thank you.

Dr. Pavlovich.

DR. PAVLOVICH: I still have trouble understanding how onerous it is to make an entire class III, although I'm told they sort of are

Class III now. And certainly if that would compromise patient care going forward and set us back 20 years and not allow people to get dialysis, that would not be appropriate. On the other hand, I know there's a push by CMS and by the NKF to get more than two-thirds of patients on fistulas and grafts.

So I think anything that would make it easier -- more difficult to get these long-term catheters lingering in patients and easier to get them, push them into fistulas and grafts into vascular access centers would be actually beneficial to the public health.

However, in trying to answer this question, I also vacillate, and I think that a reasonable case was made that if they're splitting and we can just put tunneled catheters into Class II with special controls, that I would be for that. And if we can keep the more dangerous or less studied devices like the Scribner and the subcu as Class III, then I would move for that.

DR. TALAMINI: Thank you.

Dr. Coldwell.

DR. COLDWELL: Coldwell.

I would carve out the Scribner and the subcu device and make them Class III and leave the tunneled catheters as Class II. But if you can't carve those out, as Dr. Schwaitzberg said, you have to leave them in III.

DR. TALAMINI: Dr. Moxey-Mims.

DR. MOXEY-MIMS: Marva Moxey-Mims, NIH.

I concur that if it's permissible to split them, the Scribners and

subcu's, Class III; and the others, Class II.

DR. TALAMINI: Thank you.

Dr. Gould.

DR. GOULD: Jon Gould.

I concur with the last two or three speakers. I would carve them out, if possible, and leave the Scribners/subcutaneous as III and move the others to II, and if that's not possible, we need for them all to stay as a III.

DR. TALAMINI: Dr. Woods.

DR. WOODS: Karen Woods.

I agree with Dr. Gould.

(Laughter.)

DR. WOODS: What he said.

And actually I think my comments or my thoughts about the Scribners and the subcu access are primarily related to the expertise at this table. Coming in here, I really did not understand that, and I think FDA needs, and obviously has us here, to listen to our opinions. And I think we've heard some very good thoughts and thought leaders express their opinions about this, and I think we have to listen to what's really happening out there in the clinical world.

So I would echo what Dr. Gould said, which is I would go with Class II/Class III, if we can separate out the Scribners and the subcutaneously implanted devices, and if we can't, I think we need to think strongly about

putting them all into a III. But Ms. Chauhan's comments are right on. I mean, we do not really want to impact patient access to these things; these are important devices. So I think FDA needs to give a lot of thought to how they're going to handle this and hopefully come up with a solution that will be best for the patients.

Thank you.

DR. TALAMINI: Dr. Simon.

DR. SIMON: I think they should be Class II, at least the tunnel catheters. That's just bringing them into line with current practice actually. And then to carve out for, previously mentioned, Scribner and the port should be kept as Class III.

DR. TALAMINI: Dr. Faulx.

DR. FAULX: Ashley Faulx.

I agree with Dr. Simon, and I don't really have anything further to add.

DR. TALAMINI: Dr. Sjogren.

DR. SJOGREN: Maria Sjogren.

I agree that the Class II should be for just about all of the catheters except for the subcu or the Scribner, so I defer to my nephrology colleagues.

DR. TALAMINI: Thank you.

So, Dr. Fisher, with respect to Question 4, the Panel consensus

is pretty clear that they feel that tunnel devices can go to Class II as long as the Scribner shunts and subcutaneous devices could stay in Class III, with the additional comments that you heard.

Is that adequate?

DR. FISHER: Yes. Thank you very much.

DR. TALAMINI: So I would like to ask Dr. Rutledge, our Industry Representative; Dr. Fennal, our Consumer Representative; and Ms. Chauhan, our Patient Representative, if they have any additional comments.

Dr. Rutledge.

DR. RUTLEDGE: David Rutledge.

No additional comments.

DR. TALAMINI: Thank you.

Dr. Fennal, additional comments?

DR. FENNAL: Mildred Fennal.

Thank you so much for the opportunity to join the Panel. No additional comments.

DR. TALAMINI: Thank you.

And I should add, Dr. Fisher, I meant to say this, with one strong dissenting vote from Dr. Fennal. But I'm sure you noted that.

Ms. Chauhan.

MS. CHAUHAN: Cynthia Chauhan.

I know the FDA is a regulatory agency, and I appreciate that,

but the underlying factor is always the well-being of the patients. And so I'm very hopeful that you can do the split because I believe very strongly it's in the best interest of the patients.

DR. TALAMINI: Thank you, Ms. Chauhan.

So I would like to thank the Panel and the FDA for their contributions to today's panel. Excellent work; great, creative thinking; good communication. It's really been a great day.

Dr. Fisher, final remarks?

DR. FISHER: Thank you.

I agree with Dr. Woods' initial impression of what this afternoon was going to be: It's going to be a slam dunk and we're going to be out of here in an hour; this is going to be the easy one. The fact that it wasn't, I think, tells me and everybody on the Panel that we had a good dialogue and that we actually were able to mine down and talk about some issues.

But we came to you with a proposal and provided a justification why we think that these should be down-classified, and you listened to us and you provided your feedback. I just want to let the Panel know that we really appreciate and value your professional opinions and that we'll take them into consideration.

I'd like to thank the Panel for all their time and effort in putting it into today. It was a full day with both panels, so we're very grateful for

your time.

Dr. Talamini, thank you very much for chairing the session. Greatly appreciate it.

DR. TALAMINI: Happy to do so.

DR. FISHER: Thank you.

DR. TALAMINI: So Session II is now closed, and the June 27, 2013 meeting of the Gastroenterology-Urology Devices Panel is now adjourned.

(Whereupon, at 5:11 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

GASTROENTEROLOGY-UROLOGY DEVICES PANEL

June 27, 2013

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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CATHY BELKA

Official Reporter